Acta Medica Scandinavica

Supplementum 621

Abstracts of papers presented at The XXXVI Scandinavian Congress of Internal Medicine

June 1 – 3 1978
Oslo Norway

Edited by
P Teisberg and E Gjone

Distributed by The Almqvist & Wiksell Periodical Company Stockholm Sweden

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POSTOPERATIVE ICTERUS IN THE CARDIAC PATIENT

Thomas Bøhmer,
Dept Med B, Rikshospitalet, Oslo, Norway

Two to five per cent of patients operated with heart-lung machine develop postoperatively a cholestatic syndrome with increase in bilirubin (70 % conjugated) and only moderate increase in ASAT and ALAT The increased bilirubin level returns usually to normal within 2 5 weeks An increase in bilirubin level after the 10 postoperative day is a bad prognostic sign There are few biochemical signs of the cholestasis which was confirmed by liver biopsy

23 patients who developed postoperative icterus had a mean heart si e of 750 ml/m^2 and a cardiac index of only 2 25 l/min/m Such patients have a severely reduced cardiac function preoperatively and are susceptible to circulatory disturbances per/postoperatively

Postoperative icterus occurs more frequently in patients with mitral valve prostesis than with aortic valve or SD/VSD or coronary bypass who are all operated with heart lung machine Bilirubin elimination measured with steady state technique showed that mitral valve patients had a reduced capacity to eliminate bilirubin preoperatively ($T_{\frac{1}{2}}$ 75 150 min) compared to control group ($T_{\frac{1}{2}}$ 30 75 min)

In the cholestatic syndrome which occurs as a result of circulatory disturbances there is also a reduced ability of the reticuloendothelial system to remove endotoxins and the incomplete transport of bilirubin to the gut facilitates resorption of endotoxins from the intestine It is possible therefore that endotoxins from infections in the urinary system or airways (E coli Proteus Klebsiella) or from the normal gut will further reduce the liver function

Liver function is most likely not caused by Halothan anesthesia by virus infection (Australia antigen) or by blood transfusions Numerous blood transfusions however is an expression of the unstable circulatory situation The cholestatic syndrome is multifactoriel due to pre/per/postoperative circulatory disturbances and possibly due also to endotoxins

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In the cholostatic syndrome which occurs as a result of circulatory disturbances there is also a reduced ability of the reticuloendothelial system to remove endotoxins and the incomplete transport of bilirubin to the gut facilitates resorption of endotoxins from the intestine It is possible therefore that endotoxins from infections in the urinary system or airways (E coli Proteus Klebsiella) or from the normal gut will further reduce the liver function

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LIVER DISEASE AS THE FIRST MANIFESTATION ON INFLAMMATORY BOWEL DISEASE

S Ritland, O Fausa and K Elgjo
Medical Department A and Department of Pathology
National Hospital of Norway, Rikshospitalet, Oslo 1, Norway

Abnormal liver function tests and morphological changes in the liver are well known complications of inflammatory bowel disease occuring in about 15 % of the patients Usually the bowel disease starts several years prior to the demonstration of liver involvement Occasionally the reverse is seen We have recently observed three patients with cholestatic liver disorder found to be associated with asymptomatic ulcerative colitis At the age of ten years biliary cirrhosis was diagnosed in the first patient Her serum transaminases were slightly and the alkaline phosphatases markedly elevated Five years later pericholangitis was demonstrated in liver biopsy Further investigations revealed a symptomless chronic ulcerative colitis Chronic active hepatitis was diagnosed in a fragmented liver biopsy specimen from the second patient a 30 years old woman and this led to longlasting treatment with corticosteroids Ten years later liver biopsy showed histological changes as seen in patients with ulcerative colitis Further examinations confirmed this diagnosis By a routine checkup a 34 years old male was found to have elevated alkaline phosphatases Liver biopsy demonstrated biliary cirrhosis and subsequent investigations revealed an asymptomatic ulcerative colitis

In patients with cholestatic liver disorders and histological evidence of pericholangitis appropriate investigations for inflammatory bowel disease should be performed

LIVER BIOPSIES IN CHRONIC ALCOHOLISM ITS CONTRIBUTION TO CLINICAL AND LABORATORY DIAGNOSIS

Oyvind Digranes,
Hjellestad Flinikken, Bergen, Norway

A survey is given of the result of 220 liver biopsies in 212 men and 8 women with chronic alcoholism and clinical signs of liver disease

Cirrhosi was found in 29 patients (13 2 %) alcoholic hepatitis in 36 patients (16 4 %) fatty infiltration in 104 patients (47 3 %) 44 patients (20 %) had non spesific signs of degeneration and repair in 5 patients the liver was found normal and in 2 patients the biopsy specimen was too small for an exact diagnosis

The relationship between the liver function tests and the diagnosis is discussed Gamma GT is found to be a much more sensitive test of alcoholic liver disease than ASAT and ALAT

Adequate nutrition was found in 60 % of the patients inadequate in 40 % but good or poor diet does not seem to be of major importance with regard to whether alcoholics will develop serious liver disease or not The amount of alcohol and the duration of the abuse is most important not the kind of alcohol

Even if there are few women in this study the results indicate a worse prognosis in female alcoholics 3 of 8 had cirrhosis 2 alcoholic hepatitis and 3 fatty infiltration

Except for a 56 year old woman who got an intra abdominal bleeding and had to go through a laparatomy there were no serious complications

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HEPATIC HYDROTHORAX

S Ritland, K Osen & B Rostad,
Medical Department A, Department of Pathology and Department of Radiology, National Hospital of Norway, Rikshospitalet, Oslo 1

Hydrothorax has long been recognized as a complication of cirrhosis of the liver Its origin is not fully established Most agree that ascites forms the hydrothorax across the diaphragm either through a diaphragmatic defect or through the diaphragmatic lymphatics We have had the opportunity to study more carefully one patient with hepatic hydrothorax A thirty-eight year old female had been treated for 13 years with corticosteroids for chronic active hepatitis when ascites and right-sided hydrothorax developed For about two years treatment with salt restriction and diuretics was successful During the last months however the liver functions deteriorated Repeated thoracocentesis had to be performed due to rapidly reproducing hydrothorax

Autopsy demonstrated pleural effusion on the right side (1700 ml) but not on the left side and ascites (400 ml) No holes or defects in the right hemidiaphragm was found A 2 cm bleb was seen bulging into the pleural cavity Microscopically the inside of the bleb was covered by mesanthelium underlined by dilated lymphatics Mediastinal lymph nodes also showed lymphostasis

In this patient the hydrothorax may be due to increased transport of fluid through the diaphragmatic lymphatics from the peritoneal to the pleural cavity

ASSOCIATION BETWEEN HLA B40 AND ALCOHOLIC LIVER DISEASE WITH CIRRHOSIS

H Bell and R Nordhagen,
Krohgstøtten Department of Oslo City Hospital, Oslo and Immunological Department, National Institute of Public Health, Oslo, Norway

HLA antigens were determined in 41 patients with alcoholic liver disease The frequency of HLA B40 in 25 patients with alcoholic liver disease with cirrhosis confirmed by liver biopsy was significantly increased (52 %) in comparison with the frequency found in 153 healthy blood donors (18 %) The HLA-B40 frequency was not increased in 16 patients with alcoholic liver disease without cirrhosis (19 %) nor in a group of 16 patients with miscellaneous liver diseases (19 %) We could not confirm the previously reported association between advanced alcoholic liver damage and HLA B8 which has been taken as a support for the relation to autoimmune mechanisms The association with HLA-B40 may support the idea that individual susceptibility to the development of alcoholic liver cirrhosis is genetically determined

So far we have investigated 100 patients with alcoholic liver disease and the results obtained are confirmed

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A PROSPECTIVE STUDY OF STREPTOKINASE AND HEPARIN IN THE TREATMENT OF MAJOR PULMONARY EMBOLISM

E Ly, H Arnesen H Eie and R Hol,
Medical Department IX and Department of Radiology,
Ullevål Hospital, University Clinic, Oslo, Norway

Treatment with streptokinase or heparin was allocated randomly to 25 patients with major pulmonary embolism verified by angiography Only patients with a history of less than five days and with major embolism affecting at least one lobar artery were included

Standard doses of streptokinase or heparin were given for 72 hours and pulmonary angiography was then repeated

The severity of the pulmonary artery occlusion was interpreted by a score system devised by Miller et al (Br J Med 2 681 1971) The mean angiographic score fell 52 3 % in 14 streptokinase treated patients compared with only 20 6 % in 11 patients treated with heparin Using the Student s t test this difference is statistically highly significant ($p<0.01$) In the streptokinase group 8 of 10 patients with massive embolism (angiographic score above 20) showed substantial thrombolysis compared with only 2 of 6 patients in the heparin group

In the heparin group 1 patient died from massive embolism 15 hours after the start of treatment and in another patient who died 4 weeks later persistent massive embolism contributed to the fatal outcome

In the streptokinase group 1 patient died 3 weeks after the start of treatment from gangrene of both legs following thrombotic occlusion of the inferior vena cava

Bleeding was more common after treatment with streptokinase than with heparin but was not a serious problem in any patient The increased bleeding tendency in th streptokinase group was related to puncture or cut-down sites whereas spontaneous bleeding was equally common in the two groups

It is concluded that patients with life threatening pulmonar embolism should be offered the benefits of treptokinase

HAEMOSTATIC PROFILE IN A CLINICAL MATERIAL

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Medical Department A, Aker Hospital, Oslo 5, Norway

During 1977 1310 blood samples were analyzed as follows Thrombocyte count fibrinogen concentration Fibrin gelation test Normotest Thrombotest Activated Partial Thromboplastin Time (APTT) Antithrombin III (At), heparin, Fibrin Degradation Product (FDP) Thrombin clotting time Based on the results a coagulation profile was defined for each sample

Suspected thrombo-embolism was the most frequent reason for consultation followed by bleeding control of heparin therapy suspected disseminated intravascular coagulation (DIC) and liver disease

In verified thrombosis increased FDP was found in all but one case Subnormal At was found in some of these patients Thrombocytopenia increased fibrinolysis often with hypercoagulation were the most frequent abnormalities in bleeding patients Only two haemophiliacs were encountered In many patients generalized bleeding tendency was ruled out

Heparin levels below a defined therapeutic range (0 2-0 7 U/ml) were found in more than half the samples from treated patients suggesting underdosage

Signs of DIC were also encountered in samples referred because of bleeding or thrombosis The At concentration tended to decrease with increasing degree of consumption coagulopathy (thrombocytopenia hypofibrinogenaemia high FDP) Occasionally subnormal At levels were found in the absence of frank DIC A study of the case records revealed that most of these patients had undergone hypoperfusion syndromes possibly complicated by DIC

The major value of this laboratory service is in the examination of the bleeding patient and the patient with DIC

HAEMOLYTIC ANAEMIA IN ALCOHOL ABUSE A REVIEW OF 14 CASES

F Wislöff,
Ullevål Hospital, Krohgstötten Dept , Oslo, Norway

Clinical and haematological data on 14 patients (eight women and six men) with alcohol-induced haemolytic anaemia and mild to moderate liver injury are presented Nine of the patients were obvious drinkers while five were socially well adjusted individuals in whom alcohol dependence was not suspected on admission to hospital Four patients presented with typical Zieve s syndrome Two further patients had a moderate transient stomato cytosis as assessed by microscopy of dried blood smears and by scanning electron microscopy The majority of the patients however did not fit into any of the syndromes proposed in the literature Indeed the validity of both Zieve s syndrome and the transient stomatocytosis with haemolysis" syndrome is questioned

HEPARIN TREATMENT OF DEEP VENOUS THROMBOSIS (DVT) CLINICAL VALUES OF HEPARIN ASSAYS

H A Holm, U Abildgaard and Chr Bjerkelund
Med Dep A, Aker Hospital, Oslo 5, Norway

In a multi center trial patients with phlebo graphically verified DVT are given continous heparin infusion for at least 5 days Blood samples are drawn daily for determination of heparin by 3 different methods 1) APTT - a global test reflecting heparin effect on the intrinsic system (Cephotest[R]) 2) Thrombin time and 3) An amidolytic assay for determination of heparin concentration (1) (Coatest[R]) The study is still in progress and this report is preliminary (1 Teien Thromb Res 8 1976)

Of 120 patients admitted to the trial 4 patients have suffered serious bleedings requiring blood transfusion In one pat an intrathoracic bleeding - probably caused by a thoracocentesis - contributed to a fatal outcome ? days after onset of heparin therapy Heparin was in the lower part of therapeutic range as determined by all three assays

The three non-fatal bleedings had average heparin conc (amidolytic assay) above therapeutic range (0,2 - 0 7 U/ml) APTT-values were above therapeutic range (>120 sec) two days or more in the non-fatal bleedings

1/5 of the total material had average heparin conc above therapeutic range and 1/4 had two or more APTT-values above therapeutic range

Thrombin time in patients with bleedings did not differ significantly from the rest of the material

Thrombocytopenia has been reported in a great proportion of patients receiving heparin prepared from bovine lung (2) In our study all patients are treated with heparin prepared from porcine mucosa (Heparin Nyco[R]) Thrombocytopenia has been recorded in only one patient This patient died from pulmonary embolism without signs of bleeding Other hemostatic parameters indicated consump tion coagulopathy (DIC) (2 Bell Ann Intern Med 1976 85, 155-160)

We conclude that thrombocytopenia does not seem to represent a major problem with the type of heparin used in this study

Our preliminary results indicate that amidolytic assay and APTT may be of value in monitoring heparin therapy by decreasing the risk of bleeding complications Thrombin time assay does not seem to have this property

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F Wisløff,
Ullevål Hospital, Krohgstötten Dept , Oslo, Norway

Clinical and haematological data on 14 patients (eight women and six men) with alcohol induced haemolytic anaemia and mild to moderate liver injury are presented Nine of the patients were obvious drinkers while five were socially well adjusted individuals in whom alcohol dependence was not suspected on admission to hospital Four patients presented with typical Zieve s syndrome Two further patients had a moderate transient stomato cytosis as assessed by microscopy of dried blood smears and by scanning electron microscopy The majority of the patients however did not fit into any of the syndromes proposed in the literature Indeed the validity of both Zieve s syndrome and the "transient stomatocytosis with haemolysis" syndrome is questioned

HEPARIN TREATMENT OF DEEP VENOUS THROMBOSIS (DVT) CLINICAL VALUES OF HEPARIN ASSAYS

H A Holm, U Abildgaard and Chr Bjerkelund
Med Dep A, Aker Hospital, Oslo 5, Norway

In a multi center trial patients with phlebographically verified DVT are given continous heparin infusion for at least 5 days Blood samples are drawn daily for determination of heparin by 3 different methods 1) APTT - a global' test reflecting heparin effect on the intrinsic system (Cephotest[R]) 2) Thrombin time and 3) An amidolytic assay for determination of heparin concentration (1) (Coatest[R]) The study is still in progress and this report is preliminary (1 Teien Thromb Res 8 1976)

Of 120 patients admitted to the trial 4 patients have suffered serious bleedings requiring blood transfusion In one pat an intrathoracic bleeding - probably caused by a thoracocentesis - contributed to a fatal outcome 2 days after onset of heparin therapy Heparin was in the lower part of therapeutic range as determined by all three assays

The three non-fatal bleedings had average heparin conc (amidolytic assay) above therapeutic range (0 2 0 7 U/ml) APTT-values were above therapeutic range (>120 sec) two days or more in the non-fatal bleedings

1/5 of the total material had average heparin conc above therapeutic range and 1/4 had two or more APTT-values above therapeutic range

Thrombin time in patients with bleedings did not differ significantly from the rest of the material

Thrombocytopenia has been reported in a great proportion of patients receiving heparin prepared from bovine lung (2) In our study all patients are treated with heparin prepared from porcine mucosa (Heparin Nyco[R]) Thrombocytopenia has been recorded in only one patient This patient died from pulmonary embolism without signs of bleeding Other hemostatic parameters indicated consumption coagulopathy (DIC) (2 Bell Ann Intern Med 1976 85 155-160)

We conclude that thrombocytopenia does not seem to represent a major problem with the type of heparin used in this study

Our preliminary results indicate that amidolytic assay and APTT may be of value in monitoring heparin therapy by decreasing the risk of bleeding complications Thrombin time assay does not seem to have this property

CLINICAL SIGNIFICANCE OF ANTIFACTOR Xa ASSAY

O R Odegård and U Abildgaard, Med Dep A, Aker Hospital, Oslo 5, Norway

Earlier studies have shown that antithrombin III probably is the main naturally occurring inhibitor of activated blood coagulation factor X ("antifactor Xa") Using the factor Xa susceptible chromogenic substrate Bz Ile Glu Gly Arg pNA (S-2222) (1) we have developed an antifactor Xa assay with higher accuracy than conventional antifactor Xa assays

Using this assay in a clinical material (n = 98) subnormal values were found in the following clinical conditions

1	Hereditary trombophilia	(n = 8)
2	Disseminated intravascular coagulation	(n = 1)
3	Livor cirrhosis	(n = 9)
4	Deep vein thrombosis some patients	(n =32)

In these patients there was a close correlation between the antifactor Xa values and the antithrombin III values

In three out of 15 individuals with haemophilia the antifactor Xa values were above that found in the reference material (n 88) This is possibly due to acquired Xa inhibitors developing as a result of multiple transfusions

1 Aurell L et al Thromb Res 11 595 1977

A PROSPECTIVE STUDY OF STREPTOKINASE AND HEPARIN IN THE TREATMENT OF DEEP VEIN THROMBOSIS

H Arnesen, A Heilo, E Jakobsen, B Ly and E Skaga
Medical Department IX and Department of Radiology, Ulleväl Hospital, University Clinic, Oslo, Norway

In a prospective trial 42 medical patients with a history of deep vein thrombosis of less than five days were allocated at random to treatment with streptokinase or heparin Only patients with extensive thromboses were included Streptokinase was given in a loading dose of 250 000 IU and a maintenance dose of 100 000 IU/hour for 4 days as a mean Heparin was given in a loading dose of 15 000 IU and a maintenance dose of 20 000 - 50 000 IU/day

The therapeutic results were evaluated by phlebo graphy Significant thrombolysis occurred in 71 4 % of 21 patients treated with streptokinase and in 23 8 % of 21 patients treated with heparin Using the λ^2-test for overall association this difference was statistically highly significant ($p<0\ 002$) Three patients in each treatment group experienced major bleeding two in each group requiring blood transfusion Minor bleeding and slight rise in temperature were encountered more often in the streptokinase than in the heparin group

It is concluded that patients with acute deep vein thrombosis with proximal extension of the thrombus beyond the calf veins should be offered a therapeutic trial with streptokinase

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THE PROGNOSTIC VALUE OF LOW LEVEL EXERCISE TEST AFTER ACUTE MYOCARDIAL INFARCTION

H Hämäläinen, V Kallio and I Vuori,
Rehabilitation Research Centre of the Social Insurance Institution, Turku, Finland

Ninety-six male patients (mean age 53 2 years) performed a bicycle exercise test with heart rate 110/min as breaking point four weeks after acute myocardial infarction No complications occurred For the two first postinfarction years the prognosis of the 32 patients who attained more than 40 watts without cardiac symptoms (group>40 W) was better in terms of cardiovascular mortality 1 death (3 %) compared to 11 deaths (17 %) in the 64 patients whose exercise tolerance was limited by cardiac symptoms or manifestations of cardiac dysfunction or whose peak work load was 40 watts or less Because of the small numbers the difference in mortality was not statistically significant however There was no difference in the reinfarction rate 13 % in each group The rate of previous infarction (9 % versus 25 % p<0 05), of cardiac arrythmias during hospital phase (20 % versus 38 % p<0 05) and of malignant arrhytmias (classes 3 5 in lown classification) during or after the exercise test (N S) was smaller in the > 40 watts group compared to the rest of the patients The age or the severity of infarction as evidenced by the values of ASAT LD and relative heart volume and by the rate of myocardial insufficiency during the hospital phase did not show statistically significant differences between the groups When all the patients alive (n = 84) and dead (n = 12) during the two years following-up were compared a statistically highly significant difference in the rate of malignant arrythmias (11 % versus 50 % p<0 001) during or after the exercise test was found Thus high incidence of malignant arrhythmias in exercise test seemed in this material to be connected with poor prognosis An early low level exercise test may be a usefull tool to discover part of the arrhythmias thus enabling the start of vigorous treatment leading to an eventually improved prognosis

INTRAVENOUS DISOPYRAMIDE IN THE CONVERSION OF SUPRAVENTRICULAR ARRHYTHMIAS INTO SINUS RHYTHM

P V Luoma, P A Kujala and J T Takkunen,
Department of Internal Medicine University of Oulu, Oulu, Finland

Cardiac arrhythmias often constitute a very important therapeutic problem that must be treated effectively Disopyramide is an antiarrhythmic agent that is structurally unrelated to any of the conventional antiarrhythmic compounds In the present trial we studied the usefulness of intravenous disopyramide in the conversion of supraventricular arrhythmias into sinus rhythm Fifty seven hospitalized patients without manifest cardiac decompensation were treated on 72 occasions for acute or recent atrial fibrillation or flutter or for supraventricular tachycardia Patients weighing 70 kg or less received 100 mg disopyramide phosphate and patients over 70 kg 150 mg of this drug by intravenous infusion over a 5 minute period unless the desired effect occurred earlier The over all success rate in the treatment of 53 cases of atrial fibrillation or flutter was 42 per cent The duration of atrial fibrillation significantly affected the efficacy of disopyramide Atrial fibrillation or flutter that had lasted less than 24 hours was treated successfully in 55 per cent of cases The over all success rate in the treatment of 19 cases of supraventricular tachycardia was 68 per cent

Disopyramide har no significant effect on blood pressure and no serious side effects were seen In patients with atrial fibrillation or flutter in which the arrhythmia was not converted into sinus rhythm diso pyramide produced an increase in heart rate The main subjective complaint of the patients was dryness of the mouth that can be attributed to the anticholinergic effect of the drug It occurred in five out of 72 cases

In the indications and the dose regimen employed intravenous disopyramide appears to be very useful of rapid action and well tolerated

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PROGNOSTIC INDEX FOR EARLY DISCHARGE IN ACUTE MYOCARDIAL INFARCTION

E B Madsen, S Rasmussen and T L Svendsen,
Cardiological Department, Glostrup Hospital, Denmark

For the purpose of selecting patients with acute myocardial infarction (AMI) for early discharge from hospital 332 patients monitored for at least 21 days in a coronary care unit were studied A new multivariate regression analysis with the survival time as the prognostic end point was utilized (Cox model)

The prognostic variables occurring in the first 5 days of admission were age sex localization of AMI aspartat aminotransferase (ASAT) maximum and area values lactic dehydrogenase (LHD) maximum value congestive heart failure acute pulmonary oedema cardiogenic shock cardiac arrest ventricular or supraventricular tachycardia ventricular premature beats atrioventricular block of second or third degree nodal rhythm bradycardia atrial fibrillation and bundle branch block

Only 4 variables made a significant contribution to the prognosis during the rest of the admission congestive heart failure (HF) cardiogenic shock (CS) atrio ventricular block (AV) and age

The prognostic index for an individual patient could be calculated by inserting the relevant prognostic variables in the following equation

$$S \quad 0\ 5\ 1\ 6 \times \begin{bmatrix} 0 & HF \\ 1 & HF \end{bmatrix} \ 1\ 0 \times \begin{bmatrix} 0 & CS \\ 1 & CS \end{bmatrix} \ 1\ 2 \times \begin{bmatrix} 0 & AV \\ 1 & AV \end{bmatrix} \ 0\ 03 \times \text{age}$$

The chance of survival of an individual patient (p_s) with index S in relation to the whole group of patients (P_o) on different days *after the fifth day was* $P_s = P_o \exp S$ The more negative S the better the prognosis The correlation coefficient between prognostic index S and survival time was 0 5 With increasing index from 1 to 3 5 the probability of surviving the 1st day decreased from 98 7 % to 9 %

Individuali ed early discharge could be proposed on the basis of this prognostic index With a risk of dying from the dis harge to day 30 below 5 % patients with S below 0 6 could be discharged at day 6 with S below 0 3 at da 9 with S below 0 1 at day 1 with S below 0 at day 15 and S below 0 4 at day 18

This model is now tested on a new larger group of p tients

LONG-TERM PROGNOSIS AFTER SURGICAL CORRECTION OF COARCTATION OF THE AORTA

K Forfang, H Rostad and S Sørland,
Rikshospitalet, Oslo, Norway

Up to 1973 356 patients were operated on for coarctation of the aorta in our hospital There were 13 operative deaths (3 7 %) A follow-up study was performed in the years 1975 to 1977 mean follow-up period 12 years (range 2 to 28 years) Of the 305 survivors, 301 answered a questionnaire on subjective symptoms and in 294 cases results from a physical examination were obtained Further examinations were performed in patients with symptoms and/or abnormal findings

At follow-up 70 8 % felt completely well without symptoms 26 2 % were slightly disabled, whereas 3 % were severely disabled Hypertension was found in 51 2 % of the patients aged > 13 years at operation as compared to 28 6 % in the younger age group Recoarctation was found in 30 patients the incidence being highest among those who were operated on under 3 years of age Aortic valve disease was present in 31 patients 29 of the 38 late deaths were caused by cardiovascular disease 4 of whom by dissecting aneurysm of the ascending aorta 12 patients died suddenly and unexpected At the follow-up aneurysm of the ascending aorta was detected in 4 patients with postoperative hypertension Bacterial endocarditis had occurred in 4 patients with one death

Both before and after coarctectomy prophylaxis against endocarditis should be given Life-long follow up with a view to recoarctation hypertension and aortic valve disease is needed in all patients Postoperative angiographic examination of the aorta is recommended

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CARDIAC ARRHYTHMIAS IN PATIENTS WITH ACUTE *CEREBROVASCULAR DISEASE*

K Miah, M Britton, U de Faire, C Helmers, C Ryding and O P Wester,
Department of Internal Medicine, Serafimerlasarettet, Stockholm, Sweden

It is well known that cerebral lesions may induce cardiac arrhythmias However indications for continuous ECG monitoring in patients with acute Cerebrovascular Disease have not been agreed upon

In 100 consecutive patients mean age 73 years, admitted to a medical stroke unit 24 hour Holter recordings were made as soon as possible after admission Only 30 per cent of the patients had no previous cardiac disease 81 patients had cerebral infarction 8 cerebral hemorrhage 9 transitory ischemic attack and 2 patients had non defined cerebrovascular disease

Only 18 patients showed no arrhythmias during the ECG-recording 23 patients had chronic atrial fibrillation and another 2 paroxysmal atrial fibrillation Bradycardia was a rare finding Ventricular ectopic activity was noted in 42 of the 77 patients (55 per cent) without atrial fibrillation In 10 patients serious forms of ventricular arrhythmias were registered 3 of these patients had acute myocardial infarction at the time of recording and they all died Congestive heart failure was a common finding in the rest of these patients

Corrected QT-interval (QT_c) was calculated in 69 patients without atrial fibrillation or Bundle Branch Block QT_c was increased in 46 patients (67 per cent) There was no significant association between an increased QT_c and ectopic ventricular activity

Conclusion Concomitant heart disease is frequent in patients with cerebrovascular disease Close observation for cardiac complications mainly congestive heart failure but also acute myocardial infarction is necessary and continuous ECG surveillance may be indicated in such high risk patients

EVALUATION OF LEFT VENTRICULAR FUNCTION BY ECHOCARDIOGRAPHY

O A Nesje and K O Levorstad,
Laboratory of Cardiology, Medical Department B and
Department of Radiology, Rikshospitalet, Oslo, Norway

The non invasive assessment of left ventricular (LV) function by echocardiography (Echo) is of great practical interest to the cardiologist In the present study the ejection fraction (EF) of the LV i e the relationship between stroke volume (SV) and end diastolic volume (EDV) EF % SV/EDV x 100 (normal value > 55 %) was determined by measuring the transverse diameter of the LV during diastole and systole by single beam M mode Echo in 67 adult patients The results were compared with the EF calculated from LV angiograms (Angio) obtained during catheterization

In 51 patients with coronary heart disease (CHD) Echo EF (range 32 76 %) related significantly with Angio EF (range 14 82 %) with r 0 73 and p < 0 001 Echo tended to overestimate EF in 6 patients with aneurysms of the anterior wall of the LV (range 36 51 % mean 46 %) compared to EF determined by Angio (range 14 46 % mean 28 %) When these 6 patients were excluded from the CHD group the statistical relationship increased to r = 0 80

In 16 patients with mitral insufficiency Echo EF (range 56 94 %) related significantly with Angio EF (range 40 88 %) r 0 62 p < 0 01 In 20 patients with mitral stenosis however there was no statistical relationship between Echo EF (range 44 76 %) and Angio EF (range 53 85 %) r = 0 20

The study shows that it is possible to assess LV function by Echo in adult patients Because its sound beam transverses the LV approximately along the minor axis just distal to the mitral valves single beam M mode Echo is not able to demonstrate an aneurysm of the anterior wall of the LV But even in these patients Echo correctly pointed to an impairment of LV function The sound beam furthermore crosses the LV in a direction perpendicular to the ANGIO plane and it is therefore not suprising that the results of the two methods differ when the geometr and the contraction pattern of the LV are altered as in mitral stenosis

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BLOOD PRESSURE DURING THE ACUTE PHASES OF CEREBROVASCULAR DISEASE

U de Faire, M Britton, C Helmers and P O Wester, Department of Medicine, Serafimerlasarettet, Stockholm, Sweden Department of Medicine, Regionsjukhuset, Umeå, Sweden

The present investigation was carried out to study the reaction of blood pressure during the course of an acute cerebrovascular stroke

In a material of 100 patients 68 women (mean age 74) and 32 men (mean age 71) consecutively admitted to the stroke unit at Serafimerlasarettet in Stockholm blood pressure (BP) was measured every sixth hour during the first three days of hospital stay and every twelfth hour from then on Patients on anti-hypertensive treatment on admission maintained their medication during the hospital stay New therapy was not initiated About one half of the patients (53 %) exhibited a history of hypertension

On admission mean BP was 177/94 for females and 174/94 for males many of them had substantial BP elevations (35 % ≥195/≥110) During the first three days of hospital stay there was a gradual decrease in both systolic and diastolic BP but from then on BP levels were relatively constant

On the fourth day in the unit mean of BP was 161/84 for females and 151/84 for males The proportion of patients with BP levels ≥195/≥110 now was small (10 % females and 7 % males)

In conclusion our data show that there is a spontaneous regulation of BP elevations in most cases during the acute phase of a cerebrovascular stroke This must be taken into account when antihypertensive treatment is considered in patients with acute cerebrovascular stroke

HYGROTON(R) IN ESSENTIAL HYPERTENSION EFFECT OF HYGROTON ON CARDIAC OUTPUT RENAL PLASMA FLOW, RENIN AND ALDOSTERONE

D Falch and A Quist Paulsen,
Hormone- and Isotope Laboratory, Aker Hospital, Oslo, Norway

The effect of *chlorthalidone (50 mg/day)* on the central and renal circulation plasma renin activity (PRA) and plasma aldosterone (PA) was studied in 11 patients (aged 37-64 years) with essential hypertension using radioisotope techniques

After 4 months of treatment (4M) the changes from the control measurements (C) were for mean arterial blood pressure (MAP) cardiac index (CI) stroke index (SI) total peripheral resistance index (TPRI), body weight (BW) plasma volume (PV) PRA and PA effective renal plasma flow (ERPF) serum sodium (Na) potassium (K) and chloride (Cl) as follows (mean ± SEM)

MAP (mmHg)	C 4M	126 ± 2 108 ± 2*	ERPF ($ml/min\ m^2$)	C 4M	229 ± 19 211 ± 13
CI ($l/min\ m^2$)	C 4M	3 571 ± 0 210 3 078 ± 0 115	Na^+ (nmol/l)	C 4M	139 5 ± 1 ? 141 0 ± 0 9
SI ($ml/beat\ m^2$)	C 4M	55 ± 3 48 ± 3	K^+ (nmol/l)	C 4M	3 9 ± 0 1 3 9 ± 0 1
TPRI ($10^5\ N\ s\ m^{-3}$)	C 4M	2957 ± 236 2843 ± 140	Cl (mmol/l)	C 4M	105 6 ± 1 2 101 8 ± 0 8
BW (kg)	C 4M	86 7 ± 3 1 85 0 ± 3 1	PRA ($nmol\ A_1/l\ h$)	4M	0 84 ± 0 21
PV (ml/cm)	C 4M	20 4 ± 0 9 20 4 ± 0 9	PA (pmol/l)	C 4M	255 ± 23 298 ± 30

* = <0 05

MAP fell concomitantly with a fall in SI and BW There were a slight but insignificant decrease in TPRI and in ERPF PRA increased K fell while PA increased insignificantly indicating that the low K counteracted the stimulation of PA by the activated angiotensins During *Saralasin* infusion (angiotensin-II blockade) after 4 months of treatment there was a negative correlation (r= -0 78) between *the change* in MAP and PRA - increment *during Hygroton treat*ment indicating that the activated renin angiotensin axis counteracted the blood pressure lowering effect of Hygroton

INDUCTION AND INHIBITION OF INJURY TO HUMAN ENDOTHELIAL CELLS IN CULTURE MEDIATED BY PLASMA LIPOPROTEINS

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Endothelial cells derived from the vein of human umbilical cords were used in experiments after 3-10 days in culture Cellular injury was evaluated by use of a ^{51}Cr release assay and phase contrast microscopy Injury induced by low density lipoproteins (LDL, d = 1 019 1 063) LDL accelerated ^{51}Cr release from endothelial cells to culture medium during 48 h in culture if the ratio between LDL cholesterol concentration and the amount of infranatant proteins in the culture medium exceeded a certain figure Increasing the LDL cholesterol concentrations without changing a normal LDL/infranatant protein ratio did not harm the cultured cells The first morphological signs of injury observed were an increased number of cytoplasmatic ramifications The cells rounded up and detached from the culture dish HDL did not injure the cells within physiological concentrations (0 400 ug HDL cholesterol/ml medium) The injurious effect of LDL was not cell specific as normal as well as LDL receptor negative fibroblasts were injured by LDL

Inhibition of the LDL induced cellular injury by high density lipoproteins (HDL, d = 1 090 1 21) Addition of HDL in amounts to give a physiological ratio between LDL and HDL in the culture medium significantly decreased the injurious effect of LDL Increasing the LDL/HDL ratio further decreased the protective effect of HDL When HDL was replaced by human albumin approximately 60 times more serum albumin than HDL (calculated in moles) was necessary to obtain the same protection against LDL induced injury

ANGIOTENSIN-II BLOCKADE (SARALASIN) IN COMBINATION WITH RENOGRAPHY IN THE DIAGNOSIS OF RENOVASCULAR HYPERTENSION

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Saralasin an angiotensin-II analog produced by Eaton Laboratories was kindly given to us for clinical trial The typical response is a lowering of blood pressure (BP) during i v infusion in renin dependant hypertension

In the daily routine for the diagnosis of renovascular hypertension Saralasin has been used in combination with a quantitative renographic technique (determination of effective renal plasma flow - ERPF) measurement of plasma renin activity (PRA) and plasma aldosterone (PA)

The diagnosis of renovascular hypertension is based on lateralization in renal vein renin activity

In essential hypertension Saralasin elicits a fall in ERPF an increase in PA a transient increase in BP while PRA is unchanged Except for the response in BP these effects are similar to those of angiotensin-II In these respects the angiotensin-II analog acts as an agonist

In renovascular hypertension Saralasin gives a pronounced lateralization and increase in ERPF and renal vein renin activity increase or fall in PA and a rapid fall in BP These effects are explained by displacement of angiotensin-II from the receptors by Saralasin

In conclusion Saralasin is a valuable tool in combination with measurement of ERPF PRA PA and BP in the diagnosis of renovascular hypertension

METABOLIC C3 STUDIES IN MAN

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Immune complexes often activate the complement system which can be considered the most important effector pathway of humoral immunity In certain disease states immune mechanisms may be of pathogenetic importance and this may be reflected by altered metabolism of complement components We have studied the metabolism of highly purified and biologically active C3 The J^{125} labelled C3 was injected together with J^{131} labelled albumin as control protein into 20 normal individuals and a material of patients of different categories Plasma radioactivity was recorded in samples taken after 10 minutes 5 hours and thereafter daily for one week Radioactivity was determined in 24 hour aliquots of urine for the same period of time Fractional catabolic rates synthetic rates and half lives were determined on the basis of these data

We found that different batches of C3 to some extent behaved differently in the initial part of each study and as compared with albumin plasma volume determined by labelled C3 tended to give too high values The isolated C3 although in its native form by biochemical criteria may partly have undergone conformational changes The results obtained in the first part of each study should therefore be interpreted with caution Mathematical and computerized analysis of data from the latter part of each study however yielded rather narrow limits for fractional catabolic rates and half lives in normals and the method may be useful in evaluating immunological activity in disease

OBESITY IN RELATION TO SMOKING
A CROSS-SECTIONAL AND LONGITUDINAL STUDY OF WOMEN IN GOTEBORG, SWEDEN

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The purpose of the present paper is to analyze the effect of smoking on obesity and the effect of cessation of smoking on body weight from quantitative aspects considered to be of special importance for physicians treating and preventing diseases related to cigarette smoking A random sample of middle-aged women in Göteborg was studied in 1968-69 (participation rate 90 1 %) and re studied in 1974-75 (participation rate 80 3 %) The women were divided in two age groups 38-46 and 50-60 years Current smokers were significantly leaner than non-smokers (2 0 kg and 3 5 kg in the respective age groups) Non smokers and heavy smokers (> 20 cigarettes per day) were significantly heavier than moderate smokers (2 6 kg and 3 2 kg in the respective age groups and 5 4 kg and 1 2 kg in the respective age groups) Heavy smokers consumed alcoholic beverages significantly more often and were significantly less active during leisure time The women who quit smoking between the two studies gained weight with 3 7 kg on average and the women who started to smoke lost weight with 0 7 kg on average The never-smokers and the current smokers gained weight on average with 1 1 kg and 1 4 kg respectively The differences were statisticall significant

THE INOTROPIC AND ELECTROPHYSIOLOGIC EFFECTS OF DIGITOXIN COMPARED TO DIGOXIN IN THE DOG HEART IN SITU

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The effects of a single intravenous dose of digitoxin or digoxin were tested in 27 pentobarbital anaesthetised Labrador dogs for 8 hours Since 2 0 mg digoxin caused continous arrhythmias in 2 dogs consistent with earlier findings by Barr et al 1972 the dose 1 0 mg digoxin was compared to 0 mg digitoxin The inotropic effect was determined by peak dp/dt from left ventricular pressure curves in 12 dogs In these dogs and two others the effects on the specialized conducting system and refractoriness in the right atrium and the AV node were measured by His bundle registration and programmed electrical stimulation Monophasic action potentials (MAP) were obtained from the right ventricle at spontaneous and constant paced heart rate in 13 dogs

Digitoxin and digoxin caused a rapid increase in contractility 10 min after the injection of the drugs The median response after 2 min was slightly higher after digoxin but this difference was not significant The median maximum response was reached after 120 and 90 min with values 102 % and 47 % above control values after digitoxin and digoxin After that the responses decreased steadily corresponding to the serumelimination phases of the two drugs The heart rate and AV nodal conduction and refractoriness was initially changed to the same degree by the drugs and these effects reached an early maximum after 10 15 min From 2 8 hours however digitoxin was significantly more potent in this respect

The MAP duration of the right ventricle was initially increased to the same extent by the two drugs These changes disappeared after 30 min and the MAP remained unchanged after 1 0 and 2 0 mg digoxin After digitoxin the MAP duration was increased 15 20 % 4 8 hours after the injection indicating a late increase in the absolute refractory period of the ventricles

It is concluded that digitoxin and digoxin cause similar effe ts on contractility approximately equivalent to the dose Aft r the distribution of the drugs has occurred the inotropic response is correlated linearly to serum concentrations By the same inotropic response however differences exist between digitoxin and digoxins electrophysiologic effects not correlated to serum concentrations The possible clinical implications of these findings will be discussed

DEGENERATIVE LIVER DISEASE AND ENDOCRINE DYSFUNCTION IN PATIENTS WITH PROGRESSIVE CONE DYSTROPHY

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A new syndrome of progressive cone dystrophy (total colour blindness) endocrine dysfunction and liver degeneration has been observed in 7 patients 6 of whom belonged to one kindred with a high degree of consanguinity

The eye-disorder was characterized by a progressive loss of the photopic mechanism

Four of the patients had a degenerative liver disease demonstrated by elevated transaminases unspecific parenchymal degeneration fatty infiltration and isolated liver cell necrosis in the liver biopsies

Different endocrine defects were demonstrated Three patients had repeated abortions and two were probably infertile In two patients a primary hypothyrosis and in another two low normal thyroid function with a protracted TRH (thyrotropin releasing hormone) test response indicating a hypothalamic defect were observed A defect in the ACTH reserve, as tested by Metyrapone[R] was seen in two patients

Diabetes mellitus of the maturity-onset type diabetes of the young was observed in three patients and a fourth had reduced glucose tolerance with further impairment *during pregnancy* Diabetes was seldom among the relatives but Hypertension was observed in the diabetic patients but several relatives also had elevated blood pressure

All the patients except one (the youngest) had a progressive hearing loss in four classified as neurogenous probably cochlear Among the relatives several cases of hearing defects were reported it is therefore difficult to relate this to the syndrome

Enlarged sella turcica were found in three patients, and in one of these an empty *sella* was demonstrated by surgery

EEG-changes a generalized dysrythmia with slow activity were recorded in two of the patients

The pathogenesis of this syndrome is unknown All the different lesions suggest a systemic disorder possibly a membrane defect

PENETRATION OF BENZYL PENICILLIN TO HUMAN TISSUE FLUID IN SUBCUTANEOUS WICKS AND SKIN BLISTERS

K B Hellum and V Lehmann,
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Tissue fluid suitable for time concentration studies was obtained from 4 healthy adult volunteers by a) implantation of a number of subcutaneous wicks on the back using non-traumatic surgical silk sutures and b) production of a series of skin blisters on the forearm by application of local suction

Antibiotic penetration to these fluid compartments was followed for 5 hours after an i v bolus injection of 2 mega units of benzyl penicillin (bpc) The concentration of bpc in serum wick and blister fluid were determined by an agar well diffusion method

In wick fluid concentrations of bpc were maximal after 10 minutes (viz at the first collection) and were equal to serum levels after 20 60 minutes

In the blister fluid a delayed entry of bpc was demonstrated concentrations being maximal between ½-1 hours Also the concentration in blister fluid was more sustained as compared to wick fluid in which the elimination phase more closely followed that in serum

Due to the small volume wick fluid may reflect the rapid changes in antibiotic concentrations of the interstitial fluid (shallow compartment") Skin blisters containing a larger fluid volume have features more typical of a deep compartment"

The techniques are safe and well tolerated and both types of fluid are useful for pharmacokinetic studies in humans

A PROSPECTIVE STUDY OF INTOXICATIONS WITH TRICYCLIC ANTIDEPRESSANT AGENTS (TCA)

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We have performed a prospective study of all major selfinflicted intoxications with tricyclic antidepressant agents (TCA) admitted to Med Dept 7 Ullevål Hospital in a 12 months period The study was initiated for two purposes We wanted to perform a prospective study of certain clinical and laboratory parameters and secondly we wanted to investigate whether treatment with sodiumbicarbonate upon admission to hospital could be of prophylactic value with regard to the development of the wellknown cardiac complications to the TCA intoxications The material consists of 26 patients of which 17 were women The mean age was 32 6 years The mean time lag from the probable intake of drug to hospital admission was only 5 hours The intoxications were clinically generally mild 6 being comatose and 5 semicomatose Drug levels measured in the plasma of 11 of the patients reflected this 7 having levels beneath 1000 ng/ml The correlation between anamnestic data on drug intake and measured levels in the blood was generally good the exceptions being the patients where aspiration of large amounts of tablets was performed shortly after intake We would like to emphasize particularly this point Most patients come to hospital comparatively shortly after the drug intake and intense gastric aspiration and lavage may prevent a serious intoxication The patients were acidemic upon admission the mean blood pH being 7 38 In the group (12) treated with 1000 ml of 1 4 % sodiumcarbinate mean pH was raised to 7 45 within one hour This group maintained a blood pH close to 7 42 from then on The other group (14) which did not receive bicarbonate had a pH of 7 37 after one hour and 7 40 after 12 hours Infusion of sodiumbicarbonate did not have any effect on the elimination of the drug as judged from serial measurements of drug plasma levels Cardiac complications were few and not of a serious nature Eleven patients had sinus tachycardia (120/min) upon admission Arrhythmias were recorded in 4 during the course and one patient developed a bundle branch block These preliminary results do not allow any conclusions with regard to the possible prophylactic effect of sodiumbicarbonate infusions on the development of cardiac complications

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The techniques are safe and well tolerated and both types of fluid are useful for pharmacokinetic studies in humans

ADJUVANT CYTOSTATIC CHEMOTHERAPY AFTER MASTECTOMY FOR BREAST CANCER - TREATMENT FOR ONE WEEK OR FOR ONE YEAR?

Report from The Scandinavian Adjuvant Chemotherapy Study Group by R Nissen-Meyer,
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Eleven hospitals in Finland Norway and Sweden have since January 1965 studied the effect of one single six-day i v Cyclophosphamide course (total dose 30 mg/kg) given as adjuvans to the conventional treatment of primary breast cancer To 507 patients the first injection was given few hours after mastectomy Their randomized control group included 519 patients In March 1976 this control group had 234 recurrences and 196 deaths the treatment group only 175 recurrences and 146 deaths Computed according to life table methods the differences in percent free of disease and crude survival increased gradually during the first 4 respectively 6 postoperative years and reached a plateau of about 10-11 % which was maintained at least until 10 years after mastectomy The differences mentioned were highly significant, and must be interpreted as an increase in cure rate

The effect was as good in the prognostically most favourable group as in the locally more advanced groups and as good in postmenopausal as in premenopausal cases

The side effects were negligible or mild and of short duration Consequently there is no reason to restrict this simple adjuvant treatment to high-risk cases

In a parallel series where administration of the same adjuvant chemotherapy course was delayed until 2-4 weeks after mastectomy no effect was observed

During the last two years another clinical trial (Bonadonna et al) has attracted much interest It demonstrates that adjuvant chemotherapy continued for one year can increase the diseasefree survival rate during the first 2-3 postoperative years with about 20 % In that trial 12 highdose 3-drug courses were given starting 2-4 weeks after mastectomy The distressing side effects during this year were considerable and it still remains to be seen if the observed effect represents an increased cure rate or only a delay in the appearance of clinically detectable metastases

In order to compare short-term and long-term adjuvant chemotherapy our study group has started a new series where all patients receive one short combination chemotherapy course immediately after mastectomy and one half of the stage II patients continue with such courses for one year

CORRECTNESS OF BEDSIDE DIAGNOSIS IN CEREBROVASCULAR DISEASE

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In 142 cases of acute stroke taken into a stroke unit preliminary diagnoses were made by at least one senior and one junior doctor The diagnoses were based only on the patient s history and the results of physical examination To evaluate the correctness of these bedside diagnoses the were subsequently compared with the diagnoses established after examinations and a final discussion in each case Regularly the following investigations had taken place Spectrophotometry of the spinal fluid x ray of the scull echoencephalography and brain scintigrams In 47 cases either autopsy or angiography had also been performed

Totally 61 % of the preliminary diagnoses turned out to be correct In five cases the neurological symptoms were explained by other diseases than stroke namely myo cardial infarction (2) Bell s palsy (1) brain tumour (1) and meningitis (1) The rest of the cases remained cerebrovascular although mistakes were made regarding the subgroup No special group was consistently over or underdiagnosed Among the presumed intracerebral haemorrhages only 26 % (5/19) could be verified compared to 78 % (52/68) of the suspected thromboses and 66 % (17/26) of the emboli In 19 cases the attack was thought to be transitoric and this turned out to be true in 63 %

We also studied if the degree of correctness was correlated to the clinical feeling of certainty Thus it turned out that when the bedside diagnosis had been considered fairly certain it was correct in 82 % whereas it was verified in only 46 % when it had been considered probable

To study if increasing experience gave us greater ability in this type of diagnosing we divided the material in three consecutive parts There were more mistakes made during the first period than during the second and third but the difference was not statistically significant

Despite experience great interest and literature studies it thus did not seem possible to establish a type diagnosis of cerebrovascular disease only on the basis of bedside findings

VESSEL DAMAGE CAUSED BY TOBACCOSMOKING IN HUMANS

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Tobaccosmoking is considered one of the major riskfactors in the development of atherosclerosis The connection between smoking and atherosclerosis have been pointed out by several clinical and epidemiological studies In animal experiments using exposure studies atherosclerosis as well as the development of atherosclerosis have been demonstrated using hypoxia, carbon monoxide etc The initial lesions of the vessel wall have been demonstrated using the electron microscope after a perfusion fixation of the vessel

28 patients were selected for the study Half of the patients were heavy cigarette smokers with a minimum daily consumption of 10 cigarettes The controls have never smoked The patients were healthy normal pregnant women having a normal pregnancy a normal delivery giving birth to normal children at term The specimens studied were the umbilical artery the umbilical vein and the vessels in the placenta villi Leakage of the endothelial lining broadening of the basementmembrane proliferative response of the media myocyttes and edema were characteristic findings The changes in the intima and media could be classified as both a degenerative and a reparative response to the injury In the placenta a marked decrease in vascularisation was found

YERSINIA ENTEROCOLITICA CARDITIS AS A DIFFERENTIAL DIAGNOSIS AND THE PROGNOSIS OF THIS DISEASE

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Medical Department C and The Laboratory of Rheumatic Research, The Copenhagen County Hospitals at Glostrup and at Gentofte, Denmark

Acute carditis in combination with serological signs of acute infection with Yersinia enterocolitica (Y ent) *serotype 3 and no other possible aetiology was diagnosed* in seven patients at the Copenhagen Coynty Hospitals (population 570 000) during the 2½ year period 01 01 74 01 07 76 The cardial symptom in all patients was precordial pain At the same time elevation of ESR and WBC as well as moderate elevation of coronary enzymes was seen in most patients This fulfilled 2 of WHO s 3 criterias for acute myocardial infarction The ECG-changes however in all cases were characteristic of acute pericarditis and in most cases the cardiac symptoms were preceded by gastrointestinal or flu like symptoms The course was uneventful in all patients and all symptoms disappeared in two weeks

At the follow up examination ½ 3 years later (average 1½ year) all seven patients were in physical well being Two patients however still presented a Y ent serotype 3 titre = 80 and one of these had persisting ECG abnormality

It is observed that in one half of the patients the aetiology would have been missed had not Y ent titre been measured by routine along with the ASO titre and it is therefore concluded that in the case of suspected carditis or suspected myocardial infarction with a discrepancy between clinic or enzymes and ECG changes the diagnosis Y ent carditis should be considered and Y ent antibody titre measured

SPIROMETRY IN AN URBAN NORDIC POPULATION AGED 20-70 YEARS

A Gulsvik,
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The precision and distribution of spirometric lung function variables in a two-phased stratified sample (560 men and 699 women) of the population of Oslo have been studied with a dry wedge spirometer The regression of the variables to sex, age height and smoking habits has been examined in a reference group of 124 males and 140 females

The vital capacity (VC)-, one second forced expiratory volume ($FEV_{1.0}$)- and forced mid-expiratory volume ($FEF_{25-75\%}$) values have a Gaussian (normal) distribution The $FEF_{25-75\%}$ values show three times larger intrasubject variability and twice as large inter subject variability as the VC and $FEV_{1.0}$ values The average difference between mean values estimated for the population of Oslo on one hand and mean values observed in the reference group on the other was 5 % in men and 3 % in women, and the difference increased with age

When standardized for age height and smoking habits a difference between men and women in the reference group of 17 % and 13 % was observed for $FEV_{1.0}$ and $FEF_{25-75\%}$ respectively Stepwise multiple regression analysis yielded a larger negative age regression coefficient for $FEF_{25-75\%}$ than $FEV_{1.0}$

The average difference between non-smokers and smokers within the reference group was 3 % for $FEV_{1.0}$ and 7 % for $FEF_{25-75\%}$

The dispersion of predicted values for lung function variables from different surveys is considerable Reference values of VC and $FEV_{1.0}$ derived from Nordic surveys are, in general higher than those derived from North American surveys

A TEN YEAR PROSPECTIVE STUDY OF RESPIRATORY SYMPTOMS AND PULMONARY FUNCTION IN 50 AND 60 YEAR OLDS

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From the Glostrup Population Studies of Men and Women born in 1914 The Copenhagen County Hospital at Glostrup, DK 2600 Glostrup, Denmark

Prevalence of respiratory symptoms in a total unselected population of men and women of one age group (born in 1914), living in a suburb of Copenhagen were registered with a 10 year interval at age 50 and 60 respectively Simultaneous changes in pulmonary function (VC FEV_1 and PEFR) were registered In 1964 24 % of the men and 12 % of the women reported cough and/or phlegm for at least three months of the year during the last two years This combination of answers to the British Medical Research Counsil Questionnaire on bronchitis has here been designated questionnaire positivity In 1974 the corresponding figures were 35 % of the men and 24 % of the women Although more men than women had respiratory symptoms at the entry of the study the incidence in the decennium 50 60 was of the same magnitude in both sexes Acute exacerbations of phlegm were more frequent in women than in men in both examinations and were statistically related to questionnaire positivity while this was only the case in 50 year old men The prevalence of dyspnoea did not differ in the two sexes in any of the examinations Only in men however it was statistically related to questionnaire positivity Pulmonary function tests of the age of 50 and 60 were well related to questionnaire-positivity Low values of FEV at the age of 50 and respiratory symptoms appeared to be significant risk factors for death during the decade studied

The course of symptoms in individuals between age 50 and 60 is described in 4 groups Questionnaire positivity at both examinations were associated with the lowest pulmonary function at the age of 60 while those with no symptoms at any of the examinations had significantly higher values of FEV and VC at the age of 60 The participants developing cough and/or phlegm as a new symptom between the two surveys showed intermediate values The ten year difference in FEV_1 as a percent of FEV_1 (50) was in women statistically more pronounced in the group with respiratory symptoms at both surveys than in the group without any symptoms In the men the same tendency was seen although it was not statistically significant

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TRIMIPRAMINE IN THE TREATMENT OF GASTRIC ULCER

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Forty patients with endoscopically confirmed gastric ulcers completed a double blind study comparing trimipramine with placebo during four weeks treatment The daily dose of trimipramine was 50 mg given before bedtime No serious side effects occurred

After four weeks treatment 12 of the 20 patients receiving trimipramine had endoscopically completely healed ulcers while in the placebo group only 4 of the 20 ulcers were healed (p=0 025) With regard to the patients complaints a distinct and statistically significant improvement was also observed in the patients receiving trimipramine (p 0 025)

It is assumed that the previously shown antisecretory effect of the drug together with the sedative and anti depressive effect make trimipramine a valuable drug in the treatment of peptic ulcer disease

CHOLEGENIC DIARRHOEA IN THE IRRITABLE COLON SYNDROME

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The versatile ^{14}C-cholylglycine assay combining ^{14}C measurements in breath and stool is the most sensitive routine test presently available for detecting ileal disease and bile acid malabsorption (1 3) In this context it must be emphasized that ingestion of bile acid sequestering agents such as cholestyramine dietary fibres and antacids containing aluminiumhydroxide can result in a positive assay (stool ^{14}C)

In the absence of ileal disease a positive stool test indicating bile acid malabsorption can occur in patients with lactose malabsorption, thyrotoxicosis and truncal vagotomy (but not after Billroth II gastrectomy)

In the course of the study some patients were found in whom their history and the assay suggested cholegenic enteropathy in the absence of conventional ileopathy or any other disorder allied to diarrhoea These patients originally suspected of refractory nervous diarrhoea were promptly relieved by cholestyramine The diarrhoea recurred whenever this medication was withdrawn On reexamination after one to five years persistence of the bile acid waste was evidenced by the assay (2)

1) Fromm and Hofmann (1971) Lancet 2 621
2) Pedersen and Thaysen (1976) Gut 17 965
3) Thaysen (1977) in Clinics in Gastroenterology vol 6, p 227

FIBRE TABLETS AS EFFECTIVE ALTERNATIVE TO WHEAT BRAN IN CHRONIC CONSTIPATION

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Lack of fibre in the diet is suggested to be an important cause of chronic constipation A fibre supplement in the form of wheat bran is easily available Some patients find wheat bran untasty and difficult to swallow However dietary fibre in tablet form might be better accepted by some of these patients

We compared the effect of tablets made of fibres from grain and citrus fruits (Dumovital[R] Dumex) to that of wheat bran in 20 chronically constipated patients The patients were randomly given 20 g wheat bran daily in one two months period and 12 fibre tablets daily in another two months period They were told to continue their usual diet during the trial and also to take the amount of laxatives they felt need for The patients were interviewed befor the trial and after each two months period Their stool habits laxativeintake dyspepsia and abdominal discomfort were registered on a point score scala The laxative properties of the fibre tablets were shown to be equally good as those of wheat bran Symptom score for constipation problems for the whole group became more than halved during the trial Twelve of the 20 patients could during the trial stop the intake of other laxatives The patients experienced reduction in dyspepsia and abdominal disconfort during the fibre tablet period After the trial was completed 8 of the patients said they could prefer to continue with the fibre tablets because the tablets were easier to take than wheat bran Seven patients preferred wheat bran because they thought it worked better Three patients judged both preparations as equally good and easy to take Only patients did not experience any effect from neither fibre tablets nor wheat bran

The mean intake of dietary crude fibre in this group of patients was calculated from diet histories and was found to be slightly less than that of the average Norwegian diet We also measured serum-lipids before and at the end of the trial Serum cholesterol was unchanged wherea serum tri glycerides decreased significantly (20%)

Dietary fibre supplementation is thus of value in the treatment of chroni constipation and fibre tablets are as effe tive a wheat bran

ENZYME ACTIVITIES IN JEJUNAL BIOPSIES IN PATIENTS WITH ATYPICAL COELIAC DISEASE

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In patients with coeliac disease there is frequently lack of one or more of the classical symptoms weight loss steatorrhea and diarrhea To see whether the paucity of intestinal symptoms in these atypical forms of coeliac disease could be due to preserved epithelial function of the proximal small intestine (1) we compared the activities of various enzymes in homogenates of jejunal biopsies in 8 patients with typical 9 patients with atypical coeliac disease and in 20 control patients Whereas both groups of patients with coeliac disease had significantly reduced specific activity (U/g protein) of six different brush border enzymes (lactase sucrase maltase alkaline phosphatase, γ-glutamyl transferase and leucin amino peptidase) when compared to the control patients there was no significant difference in the mean specific activity in the two groups of coeliac disease Neither was there any significant difference in the mean activities of plasma membrane enzyme (5 -nucleotidase) or lysosomal enzymes (acid phosphatase and N-acetyl-β-glucosidase)

The results do not support the hypothesis that the paucity of symptoms in atypical coeliac disease is due to preserved epithelial function of the proximal small intestine

1) D B A Silk P J Kumar J P W Webb et al
Ileal function in patients with untreated coeliac disease Gut 1975 16 261-267

CARCINOEMBRYONIC ANTIGEN (CEA) IN LIVER DISEASE AND ITS RELATION TO DIFFERENT LIVER FUNCTION TESTS

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Plasma CEA was studied in 165 patients with special emphasis on alcoholic liver diseases CEA was moderately increased In 36/109 patients (33 %) with alcoholic liver diseases the CEA value was above 4 ug/l compared with 2/41 (5 %) in the non alcoholic group In benign biliary disease 3/15 patients (0 %) had CEA above this level Our normal reference value based on 164 blood donors was 3 5 ug/l (mean + 2SD)

In patients who continued drinking the CEA level remained unchanged over long periods in contrast to patients who reduced or stopped their alcohol intake In the latter group CEA dropped from 6 7 to 4 2 ug/l during the first weeks and increased again when the alcohol consumption was resumed Lack of decrease in patients with elevated CEA values after alcohol withdrawal should arouse suspicion of a possible malignant disease

A significant correlation was found between CEA level and the level of γ GT (n=66 p<0 0) and parallel fluctuations were seen in ASAT ALAT and alkaline phosphatase

The frequency of complicating disorders was highest among the alcoholic patients Of 36 patients with CEA above 5 ug/l 27 (75 %) had complicating diseases in the respiratory or gastrointestinal tract and 25 (69 %) were smokers The best correlation between CEA and γ GT was found in patients with no concomitant disease (r=0 55 p<0 001 n 63) The increase of CEA was greatest in patients with complicating disorders

Much of the CEA increase in patients with alcoholic liver disease seems to be secondary to respiratory or gastrointestinal tract disorders This may explain why patients with alcoholic liver disease have elevated plasma CEA more often than patients with other liver affections

COMMON INTESTINAL BACTERIA IN ETIOLOGY OF COLON CANCER

T P Störtebecker,
Åkerbyvägen 282, Täby, Stockholm, Sweden

The incidence of colon cancer is higher throughout the Western industrialized world than among populations of more primitive and rural conditions (IARC)

The incidence of colon cancer does not run parallell to the incidence of gastric cancer, which contradicts that colon cancer is caused by environmental carcinogens from the food supply

Thus the cause of colon cancer has to be due to an increased production of carcinogens in the contents of the great bowel

In their metabolism microorganisms are able to synthesize polycyclic hydrocarbons and carcinogens (i a Birch & Smith, Ehrensvärd)

Both fungi as Aspergillus flavus and Geotrichum candidum and common intestinal bacteria as E coli are potent synthesizers of carcinogens

Colon cancer is common in villous polyps but very rare in flat ones (i a Morson)

A long lasting retention of microorganisms in crypts of villous polyps induces an increased biosynthesis of carcinogens

A chronic constipation so common among people of the Western world may contribute to a high production of carcinogens in the colon

Our most efficacious therapy against colon cancer may be to counteract constipation and to alter the intestinal microflora and by these means we are able to decrease the biosynthesis of carcinogens in the colon

For references see T P Störtbecker Unnecessary Cancer
Chronic Infections as a Cause of Cancer
Natur och Kultur Stockholm 1978 pp 256

CARCINOEMBRYONIC ANTIGEN (CEA) IN LIVER DISEASE AND ITS RELATION TO DIFFERENT LIVER FUNCTION TESTS

H Bell, H Orjasæter and H F Lange,
Krohgstøtten Department of Oslo City Hospital, Oslo and Immunological Department, National Institute of Public Health, Oslo, Norway

Plasma CEA was studied in 165 patients with special emphasis on alcoholic liver diseases CEA was moderately increased In 36/109 patients (33 %) with alcoholic liver diseases the CEA value was above 4 ug/l compared with 2/41 (5 %) in the non alcoholic group In benign biliary disease 3/15 patients (20 %) had CEA above this level Our normal reference value based on 164 blood donors was 3 5 ug/l (mean + 2SD)

In patients who continued drinking the CEA level remained unchanged over long periods in contrast to patients who reduced or stopped their alcohol intake In the latter group CEA dropped from 6 7 to 4 2 ug/l during the first weeks and increased again when the alcohol consumption was resumed Lack of decrease in patients with elevated CEA values after alcohol withdrawal should arouse suspicion of a possible malignant disease

A significant correlation was found between CEA level and the level of γ GT (n=66 p<0 02) and parallel fluctuations were seen in ASAT ALAT and alkaline phosphatase

The frequency of complicating disorders was highest among the alcoholic patients Of 36 patients with CEA above 5 ug/l 27 (75 %) had complicating diseases in the respiratory or gastrointestinal tract and 25 (69 %) were smokers The best correlation between CEA and γ GT was found in patients with no concomitant disease (r=0 55 p<0 001 n 63) The increase of CEA was greatest in patients with complicating disorders

Much of the CEA increase in patients with alcoholic liver disease seems to be econdary to respiratory or gastrointestinal tract disorders This may explain why patients with alcoholic liver disease have elevated plasma CEA more often than patients with other liver affections

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Much of the CEA increase in patients with alcoholic liver disease seems to be secondary to respiratory or gastrointestinal tract disorders This may explain why patients with alcoholic liver disease have elevated plasma CEA more often than patients with other liver affections

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Supplementum 622

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Department of Internal Medicine,
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CONTENTS

ABBREVIATIONS

BSA	Body surface area
MAP	Mean arterial pressure
Var	Variability of blood pressure
CO	Cardiac output
Dye	Dye dilution
Imp	Impedance cardiography
HR	Heart rate
SV	Stroke volume
TPR	Total peripheral vascular resistance
PV	Plasma volume
BV	Blood volume
ECV	Extracellular volume
IF	Interstitial fluid
GFR	Glomerular filtration rate
RPF	Renal plasma flow
RBF	Renal blood flow
RVR	Renal vascular resistance
FF	Filtration fraction
PRC	Plasma renin concentration
P aldo	Plasma aldosterone concentration

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PART I

Introduction

Blood pressure is normally distributed in the population the hypertensives being scattered to the right side of the distribution curve No justification can be found for drawing a dividing line to separate normal and elevated blood pressure Essential hypertension is viewed upon as a continuous spectrum in which each level of blood pressure ever when obtained by casual reading carries prognostic significance for the development of end-organ disease Although this is true for epidemiological studies in small-sized samples it is relevant to define blood pressure levels under controlled conditions. This restriction in particular applies to mild hypertension a condition on which many physiological studies have been focussed Mild hyper tension may represent a transitional state The deviation from the normal range in some subjects represents merely a fortuitous finding, whilst in others it proves to be the initial phase of a hypertensive process.

Some studies on so-called borderline hypertensives have been carried out in patients who had been admitted to the investigation after only a single screening and some of these were found to be normotensive during subsequent physiological studies. A run-in period is therefore necessary to come to terms with the condition

In established hypertension chicken and egg questions often arise as soon as physiological or biochemical studies yield abnormal results. Are such abnormalities contributory factors to the hypertensive state or do they reflect the impact of the increased blood pressure on the organism Despite this uncertainty such investigation can be rewarding on the strength of the assumption that deviations which are supposed to occur early are likely to be identifiable as factors participating in the elaboration of the hypertensive process whereas late abnormalities are more likely to result from the hypertensive process itself

Direct assessment of sequential changes based on follow-up studies can only be carried out in small numbers of patients who do not yet need or refuse effective treatment but who still comply to repeated investigations. The results of such an approach are presented in part III as a finishing touch to our other findings. In the large majority of patient the investigator has to make do with cross-sectional studies, coupled with indirect estimates of the duration of the hypertensive process. The following inroad should be considered here

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Firstly a direct estimation of the duration of hypertension is sometimes possible when periodic health examinations have been carried out previously This criterion at the present state of health care is far from infallible In the large majority of patients the known duration of hypertension is a mere guess because blood pressure has not been measured or recorded before.

The second best choice in interpreting cross sectional investigations is to use age as a reference frame It can be conceived that essential hypertension is rooted in early life Even if such a concept is discarded in favour of the assumption that essential hypertension is a disorder which can arise at any age a strong probability exists that hypertension in young adults has had a short history Along the same line of reasoning the higher age groups should encompass a relatively large proportion of cases of longstanding hypertension The use of age as a reference frame is subject to some restrictions First the relationships with age should be offset against the physiological impact of aging per se

Secondly it should be borne in mind that early cases keep coming in at any age and that the patterns which could be interpreted as occurring in the later stages will be diluted by a proportion of cases of maturity-onset hypertension

In order to estimate the influence of these factors the results in the last resort can be compared with those obtained in longitudinal studies The use of age as a reference frame constitutes the basis of part II A Another method of appraising the duration of the hypertensive process in cross sectional studies is to select a variable which is known to change pari passu with time as a consequence of hypertension The results of renal function studies have been used as such It should be borne in mind that this approach is fraught with substantial errors not only because of the erroneous inclusion of cases of unrecognized renal hypertension but also because of the varying severity of the hypertensive process Nevertheless we have attempt ed to interrelate different variables in order to keep track of the development of the disease (part II B)

The findings presented in parts II and III will be discussed and compared with the data from other laboratories in part IV in an attempt to establish the physiological biochemical background of the natural history of the disorder

Methods

Selection of patients

Patients were selected for the study in the out-patient department they were considered hypertensive when their blood pressure exceeded 150 mm Hg systolic or 100 mm Hg diastolic during at least three consecutive visits. None of the patients were on antihypertensive therapy during the studies If they had been treated before drugs were stopped at least two weeks before admission. The diagnosis of essential hypertension was made after exclusion of known causes of hypertension
The screening protocol consisted of intravenous pyelography isotope renography and if necessary renal arteriography None of the patients had proteinuria or excess excretion of vanillyl mandelic acid When other metabolic diseases such as diabetes hyperlipidaemia etc coexisted subjects were excluded from the study
A further prerequisite for admission was, that hypertension was still benign and uncomplicated fundal changes with a few exceptions being restricted to grade I or II
After this initial work-up patients were admitted to a metabolic ward, where they received a standardized diet containing 60 mmol of sodium per day Potassium intake was not controlled Usually the patients were in sodium balance on the fourth day of admission From then on the haemodynamic and endocrinological studies were performed during recumbency and after an overnight fast.

Blood pressure

For 24 hour blood pressure monitoring two types of automatic devices were used. Until 1974 we used a Godart haemotonograph based on the oscillometric phase shift -principle developed by De Dobbeleer (9) After 1974 blood pressure was recorded by the ,Arteriosonde (Roche) which operates through the Doppler effect (107) From the measurements the variability of blood pressure was calculated as the difference between highest and lowest reading expressed as a percentage of the highest value

$$\left(\frac{P_{max} \; P_{min}}{P_{max}} \% \right)$$

During the measurement of cardiac output intra-arterial pressure was recorded by direct manometry from an indwelling needle and a Statham transducer Systolic diastolic and mean pres ure were recorded with a Hellige multicardiotest apparatus For computation of mean blood pressure from indirect recordings the formula of McIntosh (141) was used mean arterial pressure = diastolic pressure + one third of pulse pressure
Direct blood pres ure values were presented as an average of 20 pulses. Average indirect blood pressure data were calculated from 20 recordings over a hour period during determination of other variables.

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In the last ten years several authors have compared this method with the dye dilution or isotope dilution technique and with a few exceptions good correlations were reported (4 40 41 99 108 121 174) In our hands the relation was acceptable In 15 patients from our series cardiac output was measured by the dye-dilution and the impedance technique simultaneously The values are plotted in fig 1 We have added to the figure values obtained under non-basal conditions (e g. tilting, saline loading) For the whole group of paired observations there is a weak relationship ($r = 0\ 66$ $p < 0\ 001$) There is no significant difference between the regression for the basal and the non-basal determinations. Compared to the dye-dilution method impedance cardiography appears to underestimate cardiac output slightly Total peripheral vascular resistance was calculated from the following formula.

$$\text{T P R. (dyn sec. cm}^{-4}\text{)} = \frac{\text{M.A.P (mm Hg)}}{\text{C.O (l/m)}} \times 80$$

In those patients where the two methods for cardiac output were used simultaneously the data from the dye-dilution were taken for derivation of peripheral resistance

Glomerular filtration rate and renal haemodynamics

Renal plasma flow and glomerular filtration rate were estimated by clearance techniques For both measurements a constant infusion was used The infusion clearance was calculated when plasma samples indicated a steady state between infusion and urinary excretion. For determining glomerular filtration rate (^{57}Co)-cyanocobalamine was used untill 1973 (Co)-cyanocobalamine is firmly bound to protein radioactivity of unbound material was determined by subtraction after exhaustive dialysis against 0 9% NaCl After 1973 we changed to inulin clearance inulin being measured by fermentation (197) The methods were compared in a series of 36 subjects (fig) and a weak relationship was found ($r = 0\ 77$ $p < 0\ 001$)

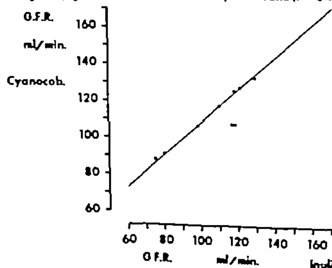


Fig Relationship between glomerular filtration rate measured by cyanocobalamine and inulin (36) 19 1 0 89x $r = 0\ 77$ $p < 0\ 001$).

Cardiac output and total peripheral vascular resistance

Cardiac output was estimated by the dye dilution technique from 1974 we also used impedance cardiography After a period during which both methods were applied together to test their congruency the impedance cardiography was used in those patients who were reluctant to undergo arterial puncture

The dye dilution technique was carried out according to the Stewart Hamilton principle A known amount of indocyanine green was injected via an antecubital vein while arterial blood was drawn with constant speed by a Harvard Pump from the contralateral brachial artery into a Kipp haemoreflectometer A direct writing micrograph BD3 (Kipp) recorded the dilution curves Calibration was performed according to the method of Sparling (177) After correction for re-circulation cardiac output was calculated by planimetric comparison of the circulation curve and the calibration curve

Impedance cardiography was carried out according to the method of Kubichek (119) Thoracic impedance data were obtained using four electrodes (aluminized tape) and the Minnesota impedance cardiograph (model 304 A)
Two electrodes are placed around the neck one around the thorax and one around the abdomen A constant sinusoidal current is applied to the upper and lower electrodes and potential changes are registrated from the two middle ones During end-expiratory breath holding these changes are thought to reflect impedance changes From the maximum rate of change of impedance stroke volume can be calculated when basal thoracic impedance ventricular ejection time and distance between the inner electrodes are known

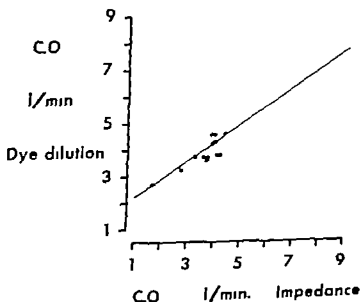


Fig 1 Relationship between cardiac output measured by dye dilution and impedance cardiography at rest and during provocative manoevres (n = 39 $y = 1.57 + 0.67x$ $r = 0.66$ $p < 0.001$)

In the last ten years several authors have compared this method with the dye dilution or isotope dilution technique and with a few exceptions good correlations were reported (4 40 41 99 108 121 174) In our hands the relation was acceptable. In 15 patients from our series cardiac output was measured by the dye-dilution and the impedance technique simultaneously The values are plotted in fig 1 We have added to the figure values obtained under non-basal conditions (e.g. tilting, saline loading) For the whole group of paired observations there is a weak relationship ($r = 0\ 66$ $p < 0\ 001$) There is no significant difference between the regression for the basal and the non-basal determinations Compared to the dye-dilution method Impedance cardiography appears to underestimate cardiac output slightly Total peripheral vascular resistance was calculated from the following formula.

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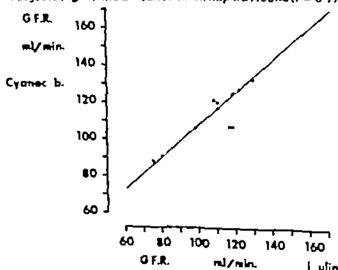


Fig Relationship between glomerular filtration rate measured by cyanocobalamine and inulin (n 36 y 19 1 0 89x r 0 77 p < 0 001)

For determination of renal plasma flow (^{125}I)-hippuran was used the infusion clearance was divided by the extraction ratio for hippuran In early reports from our laboratory a 90% renal extraction was assumed However Kolsters (116) has shown that this is an over-estimation since on the average only 74% is extracted Therefore we have retrieved and recalculated all data from earlier years on this basis Renal blood flow was calculated from the formula

$$R\ B\ F = \frac{R\ P\ F}{1 - Ht}$$

where Ht is the venous haematocrit Renal vascular resistance was then calculated as

$$R\ V\ R\ (dyn\ \ sec\ \ cm^{-5}) = \frac{M\ A\ P\ (mm\ Hg)}{R\ B\ F\ (ml/m)} \times 80\ 000$$

Filtration fraction was calculated from the quotient $\frac{G\ F\ R}{R\ P\ F}$

Plasma volume (P V)

This variable was estimated by determining the dilution of (^{131}I)-albumin (RISA) after 5 μCi was injected intravenously Blood samples were drawn at 10 20 30 and 40 min Plasma activity was extrapolated to zero time Blood volume was calculated with the formula

$$B\ V = \frac{P\ V}{1 - Ht}$$

Extracellular volume (E C V)

This variable was estimated by means of radiosulphate After intravenous injection of 50 μCi of (^{35}S)-sodium sulphate blood samples were drawn at 30 60 90 120 and 180 min The zero time value was calculated by semilogarithmic extrapolation

Plasma renin concentration (P R C)

Blood samples for renin determination were taken between 09 00 and 10 00 hours Chilled EDTA-containing tubes were used for collecting the blood which was centrifuged immediately Renin was determined according to the method of Skinner (172) An excess of exogenous renin substrate prepared from sheep plasma was added to the specimen Endogenous renin substrate and angiotensinases were destroyed by dialysis against a buffer solution at pH 3 3 Following incubation with renin substrate prepared from sheep plasma the angiotensin generated was measured by bio-assay (163 172) or later by radio-immuno-assay (165 180) The two methods were frequently compared

Plasma aldosterone

Blood was collected in the same way as for the renin assay After purification by paper chromatography aldosterone was measured by radio-immuno-assay as described by Fraser (65) Recently we started to use the CIS Aldosterone Radio-immuno-assay kit which provides a sensitive and specific determination of aldosterone on dried extracts of plasma samples without chromatography (139)

Statistical methods

Means, standard errors and correlation coefficients were calculated according to standard statistical methods. Regression analysis were carried out using the least squares method

Differences in means between two groups were assessed by the unpaired Student s t test while the paired t test was used for determining changes within groups

A p-value of less than 0 05 was accepted as being statistically significant.

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Filtration fraction was calculated from the quotient $\frac{G\ F\ R}{R\ P\ F}$

Plasma volume (P V)

This variable was estimated by determining the dilution of (^{131}I)-albumin (RISA) after 5 μCi was injected intravenously Blood samples were drawn at 10 20 30 and 40 min Plasma activity was extrapolated to zero time Blood volume was calculat ed with the formula

$$B\ V = \frac{P\ V}{1 - Ht}$$

Extracellular volume (E C V)

This variable was estimated by means of radiosulphate After intravenous injection of 50 μCi of (^{35}S)-sodium sulphate blood samples were drawn at 30 60 90 120 and 180 min The zero time value was calculated by semilogarithmic extrapolation

Plasma renin concentration (P R C)

Blood samples for renin determination were taken between 09 00 and 10 00 hours Chilled EDTA-containing tubes were used for collecting the blood which was centrifuged immediately Renin was determined according to the method of Skinner (172) An excess of exogenous renin substrate prepared from sheep plasma was added to the specimen Endogenous renin substrate and angiotensinases were destroyed by dialysis against a buffer solution at pH 3 3 Following incubation with renin substrate prepared from sheep plasma the angiotensin generated was measured by bio-assay (163 172) or later by radio-immuno-assay (165 180) The two methods were frequently compared

PART II

Results

Cross sectional study

In all 207 patients were selected for the cross-sectional study. There were 123 men (age range 17–73 years) and 84 women (age 19–73 years). The mean age was 45.5 years. Twenty six of these patients underwent follow-up studies for an average period of 5 years (Part III).

Since the entire array of determinations was not carried out in all patients, an account is presented in table 1. The individual data have been recorded in the appendix.

Table 1

Means and standard errors for the various types of investigation

Type of investigation	Number of pat. studied	Results (mean ± S.E.M.)
Mean blood pressure	173	117 ± 1 mm Hg
[illegible]4 hour B.P. recordings (variability)	58	31 ± 1%
Cardiac output		
dy. dil.	100	5.64 ± 0.15 l/m
imp. card.	99	4.96 ± 0.15 l/m
Plasma volume	182	2873 ± 40 ml
Extracellular volume	96	11.7 ± 0.79 l
Glomerular filtration rate		
[illegible]	64	1[illegible]4 ± 3 ml/m
inuline	99	108 ± 3 ml/m
Renal plasma flow	185	484 ± 1[illegible] ml/m
Plasma renin concentration	197	9.4 ± 0.4 ng/ml h
Plasma aldosterone	91	1[illegible]8 ± 1.3 ng/100 ml

borderline hypertensives as defined by Birkenhäger and Schalekamp (1?). When blood pressure is plotted against age a significant positive correlation is obtained (fig. 3; $r = 0.44$; $p < 0.001$). The scattergram comprises 173 patients, in 100 of whom blood pressure was measured intra-arterially.
There is no obvious difference in distribution of data obtained from direct and indirect estimations.
Variability of blood pressure was determined in 58 patients and showed a significant inverse relationship with age ($r = -0.33$; $p < 0.02$) as shown in fig. 4.

2. *Cardiac output*

Cardiac output was measured in 159 patients. In 100 of them the dye-dilution technique was used, while in 59 patients the impedance method was applied instead. The relation of cardiac output to age shows a wide scatter, there being no difference between the pattern of the dye-dilution and impedance date (fig. 5). Despite the marked variations, a significant inverse relationship exists between cardiac output and age ($r = -0.31$; $p < 0.001$).
The decline in cardiac output is mainly due to a reduction in stroke volume with age (fig. 6), this relation being significant ($r = -0.?1$; $p < 0.02$).
Heart rate and age showed an inverse relationship, but this was not statistically significant ($r = -0.16$; $0.05 < p < 0.10$).

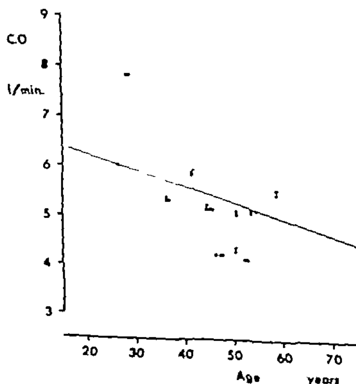


Fig. 5. Relationship between cardiac output measured by dye dilution (closed circles) or impedance cardiography (open circles) and age. For the whole group ... 6.9 ... 0.03x (n = 159; ... 0.31; p ... 0.001).

A Relationships with age

In this paragraph we will present the haemodynamic and volume estimations as raw data without conversion to standard body surface area since no differences in B S A could be detected with increasing age

1 *Mean blood pressure*

Although blood pressure was measured in all patients in 34 of them only infrequent readings were obtained at the time of the haemodynamic investigations These patients were omitted from this section A minority of the patients was normotensive at the time of the haemodynamic studies they represent the group of

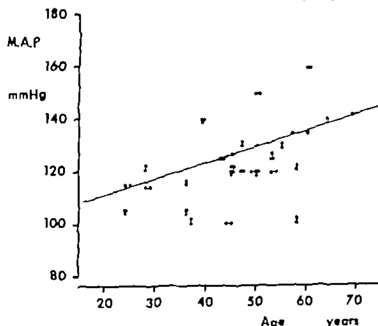


Fig 3 Relationship between mean arterial pressure and age Blood pressure was measured intra-arterially (closed circles) or indirectly with an Arteriosonde (open circles) Regression analysis yields for the whole group y = 98 + 0 63x (n = 173 r = 0 44 p < 0 001)

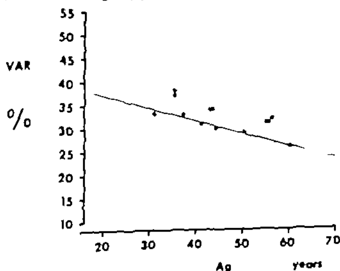


Fig 4 Relationship between 24-hour variability of blood pressure and age (n = 58 y = 4 – 0.26x r = –0 33 p < 0 0?)

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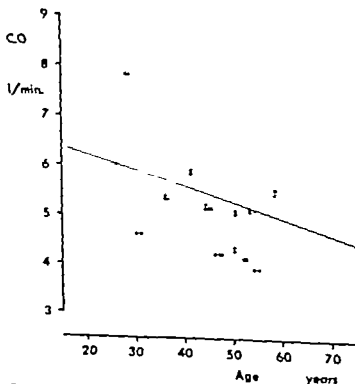


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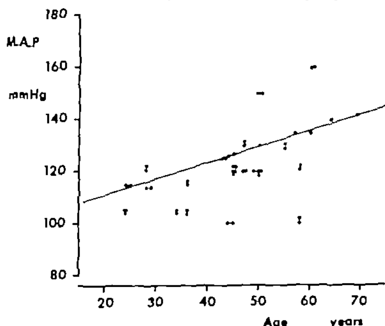


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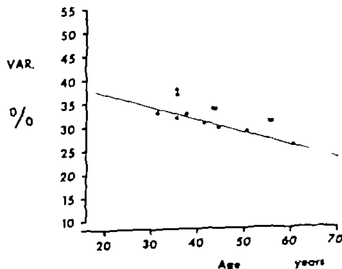


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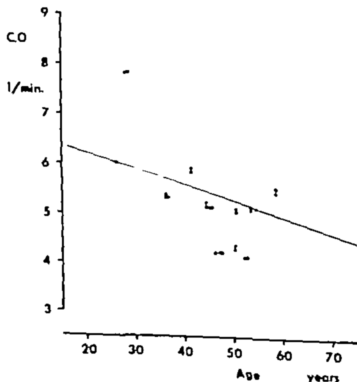


Fig 5 Relationship between cardiac output measured by dye dilution (closed circles) or impedance cardiography (open circles) and age For the whole group y = 6.9 0.03x (n = 159 r -0.31 p < 0.001)

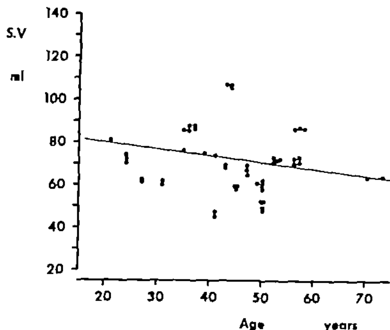


Fig 6 Relationship between stroke volume and age (n = 138 y = 86 − 0.30x r = −0.21 p < 0 0?)

3 *Total peripheral vascular resistance*

This variable could be calculated for the 159 patients in whom cardiac output was measured In 100 patients intra arterial blood pressure determinations were available and *in the remaining 59 patients the indirect readings from the Arteriosonde* were used

Total peripheral resistance gradually rises with age (fig 7) the relationship being significant (r = 0 41 p < 0 001)

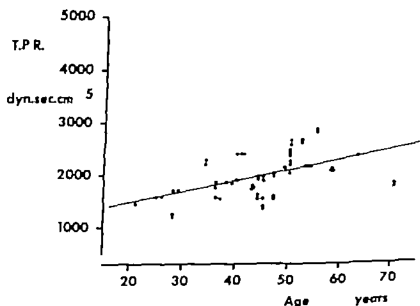


Fig 7 Relationship between calculated total peripheral resistance and age Closed circles represent calculations from intra-arterial observations open circles represent indirect measurements. *For the whole group y = 1079 + 1x* (n = 158 r = 0 41 p < 0 001)

4 *Plasma volume and blood volume*

These variables were measured and calculated in 182 patients. The data are scattered over a wide range and there is no relation between plasma volume or blood volume and age.

5 *Extra cellular volume*

This variable was measured in 96 patients and showed no relation with age

6 *Glomerular filtration rate*

In a total of 163 patients glomerular filtration rate was determined in 64 subjects by means of cyanocobalamine clearance and in 99 by inulin clearance Glomerular filtration rate tends to fall gradually with age (fig. 8 $r = -0.21$ $p < 0.01$)

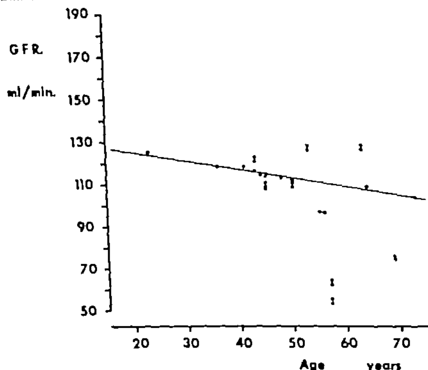


Fig 8 Relationship between glomerular filtration rate measured by inulin (closed circles) or cyanocobalamine (open circles) and age Regression analysis yields $y = 133 - 0.42x$ (n = 163 –0 1 p 0 01)

7 *Renal plasma flow and renal blood flow*

The results are presented in fig 9 These variables were determined and calculated in 185 subjects Highly significant inverse relationships are found between renal plasma flow and age ($r = 0.53$ $p < 0.001$) and between renal blood flow and age ($r = -0.51$ $p < 0.001$) It can be inferred from these relations that renal plasma (or blood) flow in the sixth and seventh decade is reduced to about one-half of that at the age of 20 years. The renal fraction of cardiac output also exhibited an inverse relationship with age (fig 10 $r = -0.31$ $p < 0.001$)

R.P.F

ml/min

1000
800
600
400
200

20 30 40 50 60 70

Age years

Fig 9 Relationship between renal plasma flow and age (n = 185 y = 796 – 6 8x r = –0.53 p < 0 001)

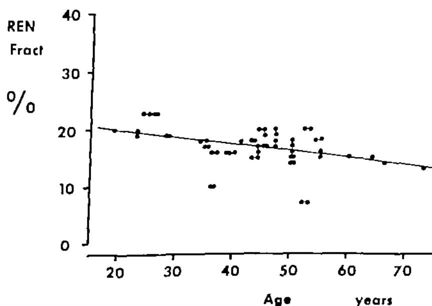


Fig 10 Relationship between renal fraction and age (n = 143 y = 23 – 0 14x r = –0 31 p < 0 001)

This variable was calculated for 158 patients. Renal vascular resistance as shown in fig. 11 increased with age ($r = 0.43$ $p < 0.001$). There is a suggestion of a curvilinear relationship with a steep increase beyond the age of 50 years. This impression is mainly caused by a small number of patients exhibiting an extremely high R.V.R.
This group was not shown to have particular characteristics apart from the exaggerated increase in R.V.R. Nevertheless we are inclined to consider these patients as a separate group an exception to the rule that R.V.R. increases with age in a linear fashion.

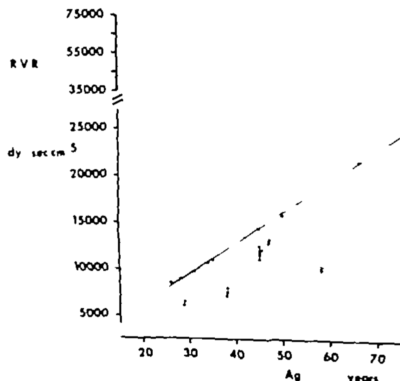


Fig. 11 Relationship between calculated renal vascular resistance and age (n 1 8) ... 3 4 r 0.43 p 0.001)

RPF

ml/min.

1000

800

600

400

200

20 30 40 50 60 70

Age years

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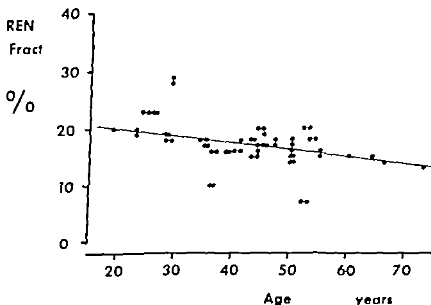


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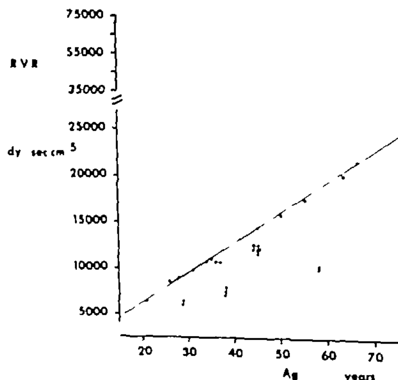


Fig 11 Relationship between calculated renal vascular resistance and age (158 y = 222 3 4 0 43 p 0 001)

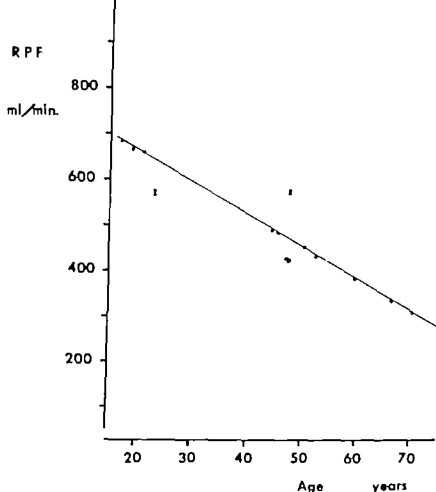


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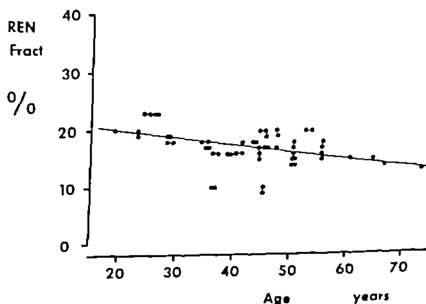


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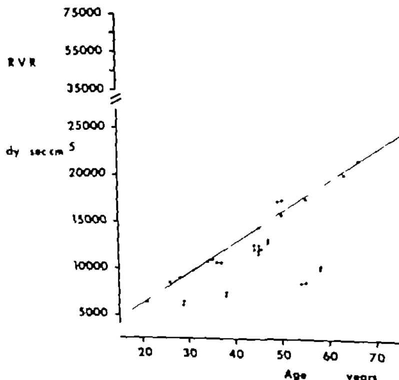


Fig. 11. Relationship between calculated renal vascular resistance and age (n = 158, y = −222 + 374x, r = 0.43, $p < 0.001$)

RPF

ml/min.

1000

800

600

400

200

20 30 40 50 60 70

Age years

Fig 9 Relationship between renal plasma flow and age (n = 185 y = 796 – 6 8x r = –0 53 p < 0 001)

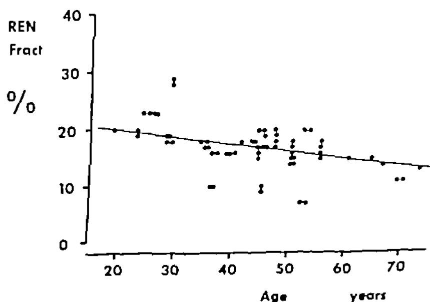


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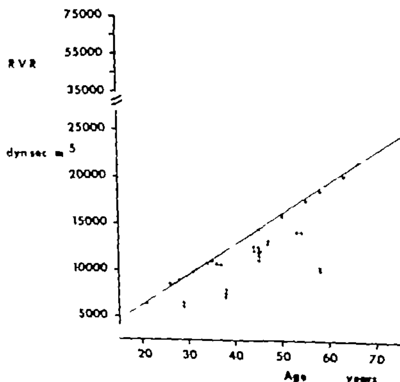


Fig. 11. Relationship between calculated renal vascular resistance and age ($n = 158$, $y = 222$ 324x, $r = 0.43$, $p < 0.001$)

9 *Filtration fraction*

This was calculated in 162 patients Again there is a positive relation with age (fig 12) which is highly significant *($r = 0\ 51$ $p < 0\ 001$)*
Five patients (2 men and 3 women) had filtration fractions which were extremely high They all belonged to the group with an abnormally high renal vascular resistance the common denominator being a severely depressed renal plasma flow

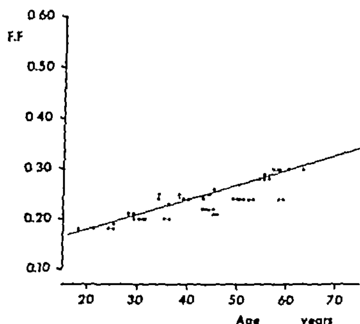


Fig 12 Relationship between filtration fraction and age ($n = 162$ $y = 0\ 12 + 0\ 003x$ $r = 0\ 51$ $p < 0\ 001$)

10 *Plasma renin concentration*

In 10 patients no values for P R C were obtained in most cases this was due to incorrect handling of material at the time of sampling or during the technical procedure Data from the remaining 197 patients are plotted against age in fig 13 There is a weak tendency for P R C to decline with age until about 50 years ($r = -0\ 20$ $p < 0\ 05$) irrespective of changes in glomerular filtration rate Low renin values are most often encountered between 40 and 60 years In patients who are older than 50 the relation of P R C with age is no longer present

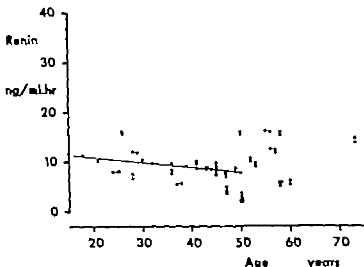


Fig. 13 Relationship between plasma renin concentration and age. A significant correlation is found only in persons below 50 years (n = 124 y = 12.9 – 0.10x r = –0.20 p < 0.05)

11 *Plasma aldosterone*

For the total of 91 observations there is no obvious relation with age (fig. 14). The values for aldosterone are within normal limits in 80 patients. In the remainder with high values we observed no development of clinical hyper-aldosteronism during follow-up in the hypertension clinic

70
60
P.Aldo
50
ng/100ml
40
30
20
10
0
20
30
40
50
60
70
Age
years

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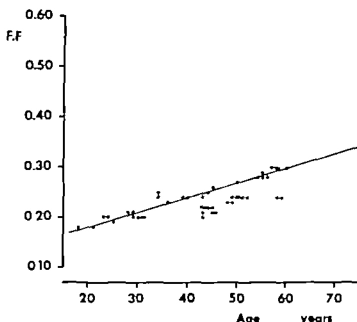


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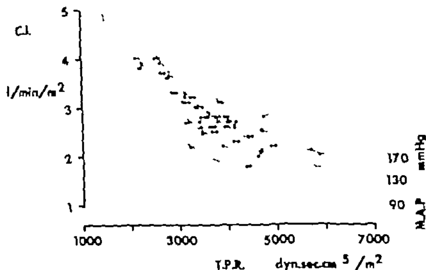


Fig. 16. Nomogram representing the balance between cardiac index calculated total peripheral resistance and blood pressure

2. *Renal haemodynamics*

Glomerular filtration rate in a particular way is directly related to renal plasma flow (fig. 17) When R.P F is lower than around 300 ml/min./m² the regression is linear ($r = 0.62$ $p < 0.001$) but above that point the slope of the regression line almost parallels the X-axis which means that at these higher flow rates G F R. is practically independent of renal plasma flow G F R is inversely related to R V R ($r = -0.57$ $p < 0.001$) as shown in fig. 18

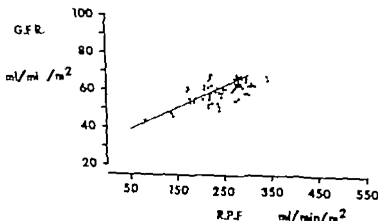


Fig. 17 Relationship between renal plasma flow and glomerular filtration rate. Up to a RPF of about 300 ml/min/m² the relation is linear ($n = 115$ $y = 33 + 0.12x$, $r = 0.62$, $p < 0.001$).

B Interrelations between variables

In order to avoid artificial relationships we converted all values presented in this section to a standard body surface area. All haemodynamic and volume data are therefore presented per square meter

1 *Systemic haemodynamics*

In fig 15 the relation between mean blood pressure and cardiac index is given At each level of blood pressure cardiac index varies widely although the range becomes narrower when pressure is higher Furthermore cardiac index shows an inverse relationship with blood pressure ($r = -0.16$ $p < 0.01$)

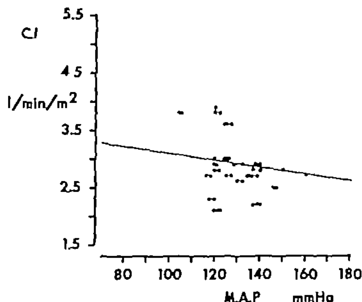


Fig 15 Negative relationship between cardiac index and mean arterial pressure ($n = 156$ $y = 3.7 - 0.01x$ $r = -0.16$ $p < 0.05$)

Since peripheral resistance is derived from M A P and C O it is strictly spoken not justified to relate this variable to the other parameters The best approach to interrelate the two independent variables and the resultant T P R appeared to be drawing them together in a three-dimensional diagram (fig 16) This figure represents the balance between flow calculated resistance and the resultant pressure The most intriguing aspect of this figure is the immense variation in the interplay between flow and resistance The higher blood pressure values tend to be dependent mainly on a high resistance

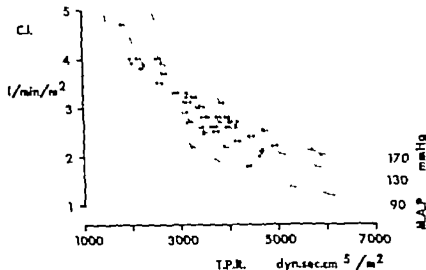


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2 *Renal haemodynamics*

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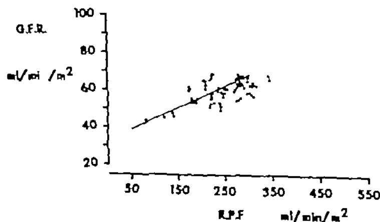


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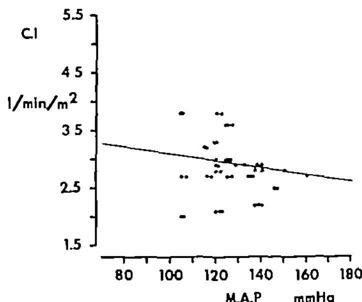


Fig 15 Negative relationship between cardiac index and mean arterial pressure (n = 156 y = 3 7 − 0 01x r = −0 16 p < 0 05)

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3 *Systemic haemodynamics vs renal haemodynamics*

There appears to be a significant inverse relationship between mean arterial pressure and renal plasma flow (r = –0.39 p < 0.001 fig 20)

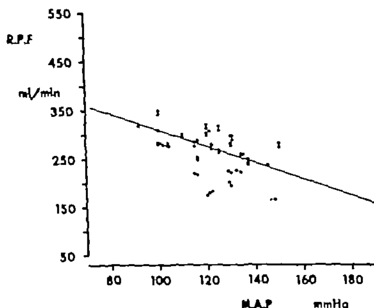


Fig 20. Relationship between mean arterial pressure and renal plasma flow (n = 158 y = 482 – 1 73x r = –0.39 p < 0.001)

To a lesser degree such a relationship was also found with respect to mean blood pressure and glomerular filtration rate (r = –0..3 p < 0.01). Filtration fraction was directly related to mean blood pressure (r = 0.45 p < 0.001 fig. 21) Cardiac output and renal blood flow were found to be positively related (r = 0.27 p < 0.005 fig 22) whereas glomerular filtration rate and filtration fraction are not clearly proportionate to cardiac output.

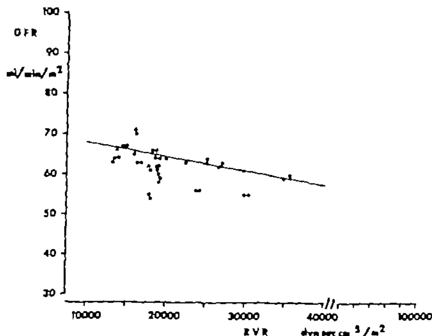


Fig 18 Relationship between renal vascular resistance and glomerular filtration rate (n = 139 y = 71 – 0 0003x r = –0 57 p < 0 001)

No comparisons were made between the other parameters of renal function because they are interdependent Nevertheless pressure flow relationships may be clarified by presenting the data on arterial pressure renal blood flow and derived resistance values in one diagram (fig 19) As in systemic pressure flow relationships a wide scatter is observed

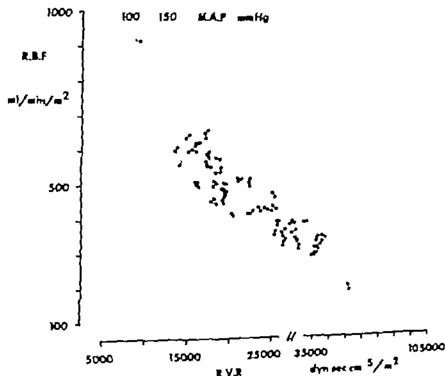


Fig. 19 Nomogram representing the balance between renal blood flow calculated renal vascular resistance and blood pressure

4 *Systemic haemodynamics vs body fluid volumes*

Plasma volume shows a weak but insignificant tendency to increase with rising blood pressure A similar direct relation is also observed between plasma volume and total peripheral resistance ($r = 0.18$ $p < 0.05$ fig 23) However these trends are predominantly caused by a few observations Blood volume and cardiac output were not related.

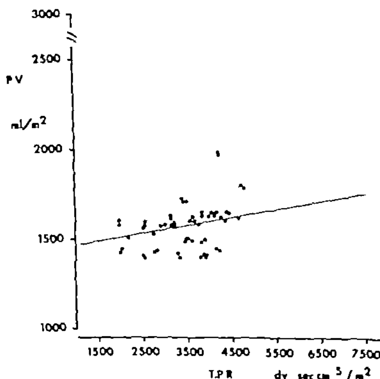


Fig 23 Relationship between total peripheral resistance and plasma volume ($n = 145$ $y = 1430$ $0.04x$ $= 0.18$ $p < 0.05$)

5 *Renal haemodynamics vs volumes*

Plasma volume is not related to renal plasma flow or glomerular filtration rate but it is directly related to filtration fraction ($r = 0.25$ $p < 0.005$)

6 *Renin vs aldosterone*

There appears to be no significant relationship between P.R.C. and aldosterone (fig 4)

FF

0 60
0 50
0 40
0 30
0 20
0 10

80 100 120 140 160 180

M.A P mmHg

Fig. 21 Relationship between mean arterial pressure and filtration fraction (n = 141 y = 0 07 + 0 0001x r = 0 45 p < 0 001)

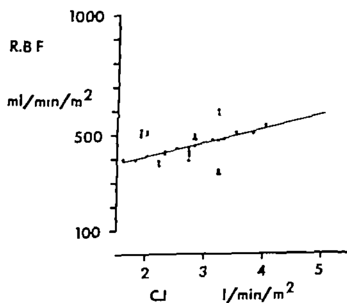


Fig 22. Relationship between cardiac index and renal blood flow (n = 143 y = 301 + 57.3x r = 0.27 p < 0 005)

7 *Renin vs systemic haemodynamics*

P R.C. is not clearly related to mean blood pressure (fig. 25) although a tendency towards a negative relationship was detectable in patients with intact G F R. ($r = -0\ 10$ $0.05\ p < p < 0\ 10$) Arbitrarily we considered a G F R. of less than 55 ml/min./m² as an index of depressed renal function. When patients below the age of 50 years are considered separately the relationship is no longer apparent.
P R.C. is unrelated to C.O and T P R. but here a biphasic pattern is observed. When G F R. is still intact renin tends to vary directly with C O and inversely with T.P R. but when G F R. has fallen to levels below 55 ml/min /m² the relations invert none of these trends however reached statistical significance.

8 *Renin vs renal haemodynamics*

Renin is inversely related to G F R ($r = -0\ 28$ $p < 0\ 001$) as shown in fig. 26. On the other hand renin levels are not related to renal blood flow or filtration fraction,

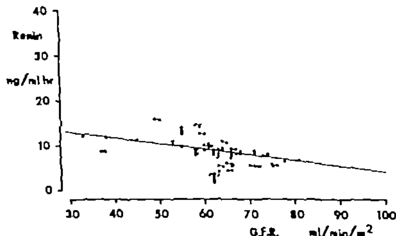


Fig. 26. Relationship between glomerular filtration rate and plasma renin concentration ($n = 160$ $y = 16\ 7 - 0\ 13$ $r = -0.28$ $p < 0\ 001$).

even when corrected for the effect of glomerular filtration rate In fig 27 the relation between renin and renal vascular resistance is given This appears to be a complex one In the whole group renin is positively related to R.V R. ($r = 0\ 18$ $p < 0\ 05$) but a distinction can be made between patients with normal and those with subnormal G F R. While the former group exhibits an inverse relation between renin and R.V R. which is bordering on statistical significance a positive though not significant relation is found in the latter group

9 *Renin and aldosterone vs body fluid volumes*

Renin and aldosterone are not related to plasma (or blood) volume however In the subgroup of patients with a reduced G F R. renin is positively related to plasma volume ($r = 0.37$ $p < 0\ 05$) but not to interstitial or total extracellular volume

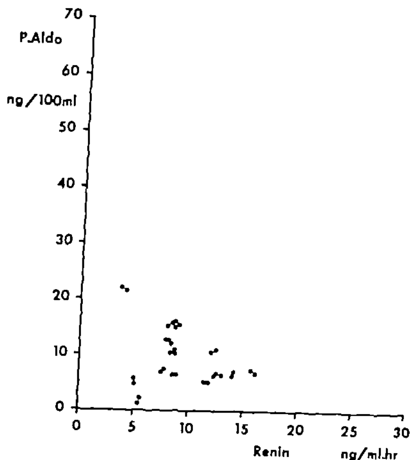


Fig 24 Plasma aldosterone related to plasma renin concentration (not significant)

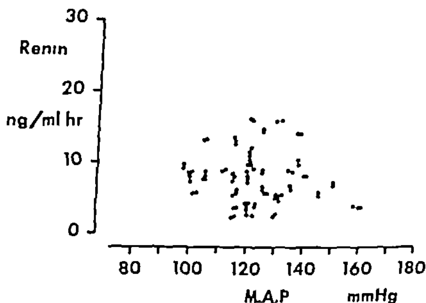


Fig 25 Relationship between mean arterial pressure and plasma renin concentration For the whole group this is a non significant relation but when only patients with a glomerular filtration rate ≥ 55 ml/min/m² are considered there is a borderline significant inverse relation

Part III

Follow-up study

Twenty-six patients all of whom were evaluated for the cross-sectional study could be followed up for an average period of 4.5 years In the course of the study myocardial infarction occurred in five patients. The uncomplicated group comprised 13 men and 8 women Mean age in this group at the start of the study was 42 years (range 25–60 years) and mean duration of follow-up was 4 6 years.
The complicated group was formed by 3 men and ? women. At the initial investigation mean age in this group was 51 years (range 44–56 years) and significantly higher than in the uncomplicated group ($p < 0.05$) Follow-up in this group on the average was 4 1 years
In both groups the following parameters were determined during the sequential studies. blood pressure plasma volume renal plasma flow renal vascular resistance and plasma renin concentration The individual date are given in the appendix In fig 28 to 3? the natural course for these patients is depicted while in table the means and standard errors are presented for the various parameters at the start of the study and after a variable period of follow-up

Table 2.

Means and standard errors for the various parameters measured during follow-up at the start of the study and after the final examination

	MAP	PV	RPF	RVR	PRC
Uncomplic. group					
start	1 4 4	1575 90	797 ± 20	21377 ± 2293	7 4 0 8
final	128 4	1985 98	290 17	25923 ± 2808	8 4 ± 0 7
	N S	N S	p < 0 05	N.S.	N.S
Complic. group					
start	14 5	1799 ± 86	297 40	23939 ± 4641	5 ± 1 4
final	145 16	1734 136	305 26	3316 ± 6615	11 ± 6
	N S	N.S.	0 05 < p < 0 10	N.S	p < 0 05

Aldosterone which is not related to mean arterial pressure shows a direct relationship of borderline significance with extracellular and interstitial fluid. It is not related to the quotient P V /I F

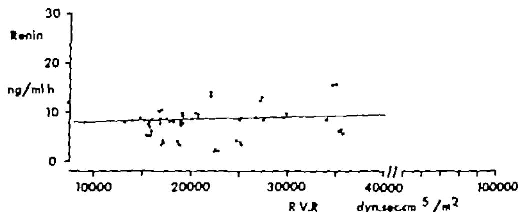


Fig 27 Relationship between renal vascular resistance and plasma renin concentration in patients with intact glomerular filtration (closed circles) and those with impaired GFR i e less than 55 ml/min/m² (open circles) While the relation seems to be negative for the first group it tends to be positive for the second For the whole group there is a significant direct relation (n = 139 y = 7 6 + 0 00005x r = 0 18 p < 0 05)

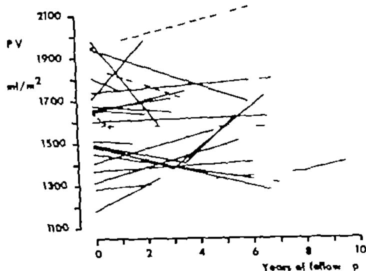


Fig. 29 Changes of plasma volume during follow-up in patients without complications (dashed lines) and in those who developed myocardial infarction (dotted lines)

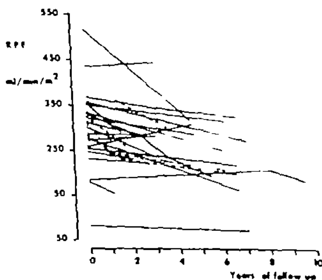


Fig. 30 Changes of renal plasma flow during follow-up in patients without complications (dashed lines) and in those who developed a myocardial infarction (dotted lines).

In the uncomplicated group no significant changes occurred in blood pressure plasma volume renal vascular resistance and plasma renin concentration although each parameter tended to increase Renal plasma flow however decreased significantly ($p < 0\ 05$)
Although mean arterial pressure plasma volume and renal vascular resistance for the complicated group at the initial study were higher than for the uncomplicated group the differance was significant only for mean arterial pressure ($p < 0\ 05$) While there was no difference between both groups in renal plasma flow at the start renin levels were slightly but not significantly lower in the complicated group
The changes in the complicated group observed during follow up showed a steeper increase in plasma renin concentration and renal vascular resistance and a more pronounced fall in renal plasma flow Due to the small number of observations and the rather wide variations in this group the changes in R V R are not significant while the reductions in R P F are only of borderline significance The increase in P R C however is statistically significant ($p < 0\ 05$)
At the end of the study mean arterial pressure plasma volume and renal vascular resistance were still somewhat higher in the complicated group although these differences were not significant Renal plasma flow was lower and plasma renin concentration was higher at this time but again the differences were not significant

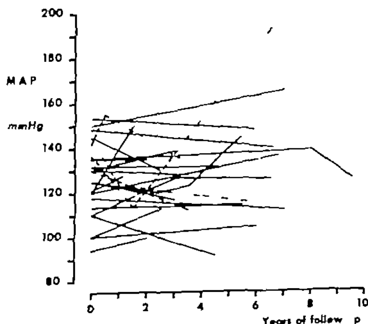


Fig 28 Changes of blood pressure during follow-up in patients without complications (dashed lines) and in those who developed myocardial infaction (dotted lines)

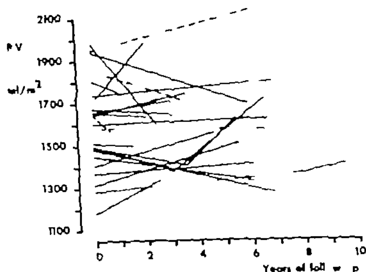


Fig 29 Changes of plasma volume during follow-up in patients without complicat (dashed lines) and in those who developed myocardial infarction (dotted lines)

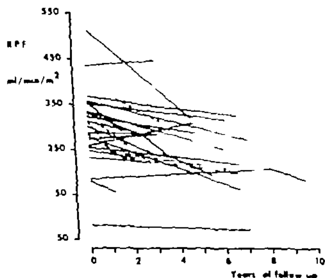


Fig 30. Changes of renal plasma flow during follow-up in patients without complic (dashed lines) and in those who developed myocardial infarction (dotted lines).

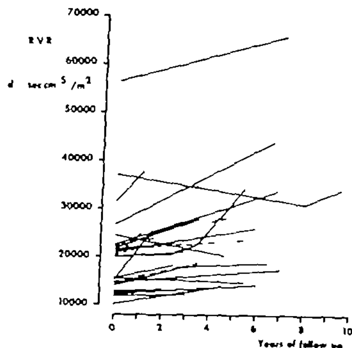


Fig 31 Changes of renal vascular resistance during follow-up in patients without complications (dashed lines) and in those who developed a myocardial infarction (dotted lines)

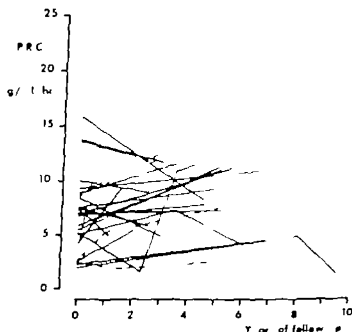


Fig. 32 Changes of plasma renin concentration during follow-up in patient without complications (dashed lines) and in those who developed myocardial infarction (dotted lines)

When alterations in the various parameters are related to each other only one significant (positive) relationship is obtained namely between changes in plasma renin concentration and in renal vascular resistance ($r = 0\,45$ $p < 0\,025$) as shown in fig. 33 This applies to the uncomplicated group only since the complicated group is too small for this kind of analysis.

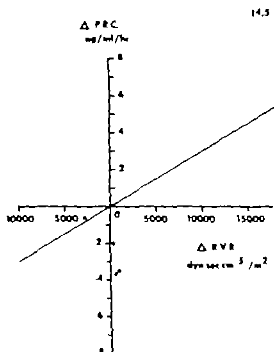


Fig 33 Changes in plasma renin concentration versus changes in renal vascular resistance during follow-up in patients with uncomplicated (closed circles) and complicated (open circles) essential hypertension. For the uncomplicated group the relation is significant ($n = 25$ $y = -0\,03 \quad 0\,0003$ $r = 0\,45$ $p < 0\,025$)

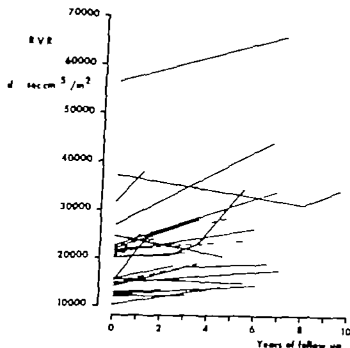


Fig 31 Changes of renal vascular resistance during follow-up in patients without complications (dashed lines) and in those who developed a myocardial infarction (dotted lines).

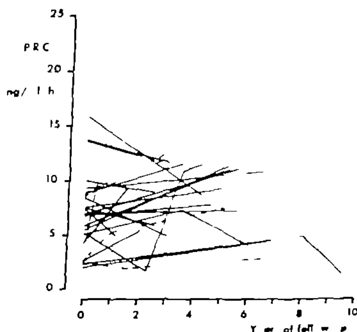


Fig 32. Changes of plasma renin concentration during follow-up in patients without complications (dashed lines) and in those who developed myocardial infarction (dotted lines)

Part IV

Discussion

Blood pressure, cardiac output and total peripheral vascular resistance

Epidemiological studies on the incidence of primary hypertension in Western countries have yielded frequencies of 15 to 20 percent (151). Obviously blood pressure is a rather erratic variable: not only are there considerable intra-individual variations during short-time observations but also age-related changes have been described. With increasing age the blood pressure tends to rise in Western culture. This upward gradient has been recognized in children as well as in adults (25, 79, 105, 110, 140, 142, 144, 206). Essential hypertension is characterized by a steeper increase with age and a more marked involvement of diastolic pressure. From our studies it is obvious that the degree of hypertension tends to be more severe in higher age groups, even though the same criterium for the diagnosis of hypertension was applied to all age groups. This feature of a progressive disorder was not obvious during actual follow-up studies. One explanation for this discrepancy may be that patients admitted to the follow-up study were not under pressure to be treated effectively because generally there was no alarming progression.
The blood pressure profile was based on systematic in-patient readings. When casual readings are taken into account, the relationship with age should be less obvious since blood pressure is accepted to be more labile in the young. We have assessed variability in a sample of patients and found indeed a significant inverse relationship between variability of blood pressure and age. Even patients with hypertension starting at a higher age apparently do not disturb this general pattern. The regression is linear: there being no apparent distinction between patients with labile or more fixed hypertension.
The incidence of labile hypertension differs in several studies, but for a great deal this seems to be due to problems of definition. Therefore, discussions on whether labile hypertension proceeds to sustained hypertension or not mainly depend on presumptions. Whereas variability of blood pressure appears to become less with advancing age the prevalence of this condition is not fully known. The natural history of labile hypertension has not been examined prospectively, although an excess risk of subsequent cardiovascular morbidity and mortality has been reported



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Blood pressure results from the interaction between cardiac output and total peripheral vascular resistance Hypertension may be the result of an increase in either one of these factors or both In the early days it was generally thought that an increase in peripheral resistance was the main factor responsible for hypertension (14 15 26 54 73 125 178 195 196 200) although some authors stressed the importance of a high cardiac output (81 131 198) In later years this high output state has been recognized in a considerable number of patients especially in those with only mild elevation of blood pressure (6 7 9 20 32 51 53 56 59 67 84 100 101 104 111 120 136 156 159 161 186 187 192 199) Although it is held by some authors that these patients form a special subgroup the available data indicate a downward trend of cardiac output during the progression of the hypertensive disease It is therefore possible that such patients represent an early stage of hypertension

In most studies the high cardiac output could be attributed to an increase in heart rate (51 53 101 104 136 158 159 161 186) stroke volume being normal In only one study an increase in stroke volume together with a normal heart rate was found (59) but in this study the patients presumably had more advanced hypertension Others have stressed an increase both in stroke volume and in heart rate although the values for stroke volume in some of the normal subjects are lower than those reported elsewhere (6 53 104 157 159)

When excess cardiac function is mainly determined by heart rate the underlying disorder has been attributed to a combination of sympathetic overactivity and parasympathetic inhibition (102 104 117) As a corollary it may be supposed that these subjects at the time of the (invasive) measurements are more easily upset than their normotensive counterparts In our laboratory all measurements are carried out after a sufficiently long time has passed for the patient to get accustomed to the environment When our determinations of cardiac output in hypertensives are compared with those in normals (mainly adapted from the literature) a marked similarity is found In fact the relation between cardiac output and age in this study does not differ much from that in normals as presented by Brandfonbrener (19) In this study equally high values for cardiac output are sometimes observed in young subjects The decline in cardiac output with age is caused by a reduction of stroke volume which also occurs in normotensives (19)

The results of our cross sectional study confirm the positive relationship of total peripheral vascular resistance and age

When the degree of hypertension is more severe cardiac output seems to fall in the face of an increase in total peripheral resistance (fig 15 and 16) which is in agreement with other studies (2 71 136 161)

It can be inferred from data in the literature that the natural history of hypertension is characterized by a steady increase in peripheral resistance (7 10 53 137 138 161)

However when the haemodynamic studies from various laboratories are studied more closely it appears that even at a stage when cardiac output is high peripheral resistance is increased at the same time (12)

Renal haemodynamics and glomerular filtration

Although renal blood flow sometimes is normal in essential hypertension (34 50 73 83 91 153 179) in the majority of patients renal haemodynamics are abnormal The general pattern is found to consist of a decrease in renal blood flow and an elevation of filtration fraction and renal vascular resistance (5 15 18 21 34 44 62, 63 66 72, 73 89 90 122, 154 173) In our patients we found evidence for a considerable impact of the hypertensive process on renal haemodynamics. The blood pressure level was inversely related to renal blood flow and glomerular filtration rate and directly to filtration fraction In the cross-sectional study we observed a negative relationship of renal blood flow with respect to age. As far as the duration of the hypertensive process is concerned the longitudinal study showed a consistent and substantial decline with time

In view of the physiological decrease in renal blood flow due to senescence (39 9? 93 114 130 153 168 169 173 197) the progressive changes in the course of hypertension should be offset against the former In normotensives no follow-up studies are available but the relationship between renal blood flow and age is well-documented

We have compared our results in the hypertensive patients with those reported for normal men (39 114 130 153 168 173 197) and found that the reduction of R.B F with age for hypertensives is generally steeper than for normal subjects. The renal fraction is normal at an early stage of hypertension but progressively diminishes with time

With a more refined technique (Xenon-washout) we could demonstrate a signific ant decrease in outer cortical blood flow already in early hypertension. This phenomenon seems to be mainly responsible for the reduction of total renal blood flow (116) The following conclusions can be drawn Firstly the results indicate that renal vascular resistance is already increased when renal blood flow is still normal Since the renal fraction is also within normal limits, it is probable that the distribution of the cardiac output to the various organs does not differ much from that in normals at an early stage of hypertension. With increasing age secondary vascular alterations develop preferentially affecting the kidneys

Changes in glomerular filtration become important only at a more advanced state, especially when renal blood flow has fallen to values below 300 ml/min./m

The findings with respect to renal haemodynamic changes support the concept of an early increase in vascular resistance as the basic hypertensive mechanism

The nature of the increase in resistance appears to be complex Both functional and structural components are recognizable The functional component of the increase in renal vascular resistance can be assessed by means of saline infusions or pharmacological studies The effects of hyperosmotic saline infusions on renal haemodynamics have been studied in our laboratory (164). Although a substantial decrease in vascular resistance could be observed the values only exceptionally decreased to the range found in normotensives. Hollenberg (94) in an attempt to discriminate between functional and structural changes infused vasodilating substances into the renal artery His experiments revealed a quantitatively important functional asoconstriction of the renal vessels in a number of patients with mild hypertension.

On the other hand structural changes have been thought to cause an increased

vascular resistance (3 64 170 171) From the work of Folkow (64) it has become apparent that in established hypertension the architecture of the vascular bed is altered the wall to-lumen ratio is increased presumably as a consequence of medial hypertrophy although it cannot be ruled out that the total number of arterioles is reduced as occurs in spontaneous hypertensive rats (95)
These findings can account for the haemodynamic status in advanced hypertension but do not entirely explain the situation in early (labile) hypertension
Although the resistance to blood flow in peripheral vascular beds at ,maximal vasodilatation was raised in borderline hypertensives thus suggesting structural changes already to be present (162) the changes in haemodynamics following physical exercise or volume expansion do not provide evidence for a decreased compliance of the vascular system (12)
Both the functional and the structural components of the increase in resistance may be the sequelae of vasoconstrictor stimuli either originating from the tissue (auto-regulation) or from increased activity on the part of pressor systems

A functional vasoconstriction has been thought to be the result of auto-regulation of tissue blood flow in response to an increased cardiac output There are several objections to this view In the first place time relations do not fit the model Whereas a substantial increase in peripheral resistance in hypertension takes many years a firm auto-regulatory control of tissue blood flow occurs much more rapidly in experimental conditions where the ability of the kidney to maintain extracellular fluid homeostasis is interfered with (8 16 29 31 42 57 58 76 78 127 129 205) In essential hypertension no direct information on such a mechanism is available Although it has been suggested that an initial rise in cardiac output is due to an increased venous return (59 190) this certainly is not due to volume expansion since plasma or blood volume in essential hypertension is normal (6 37 43 53 74 80 97 166 194) or even reduced (48 59 96 103 152 155 158 183 185 188 191) Although in the present study no comparison with normotensives was undertaken the hypertensive group per se failed to show a relationship between cardiac output or mean arterial pressure and plasma or blood volume

The most important point against autoregulation is the absence of a substantial increase in cardiac output in the younger age group
Enhanced systemic pressor activity could be based either on the renin-angiotensin system or on the adrenergic system or both Although several studies have established that values for plasma renin activity (or concentration) and aldosterone are within normal limits in most patients with hypertension rather wide ranges are found in these subjects (17 22 23 27 33 38 45 49 60 69 70 75 86 87 109 118 123 126 143 146 181) High renin levels are found in only a minority of patients with essential hypertension This already casts some doubt on the assumption that increased activity of the renin-angiotensin system plays a role in the rise of vascular resistance Moreover in about one third of patients plasma renin is abnormally low (for references see 46) In these cases renin is suppressed and unresponsive to stimuli as sodium restriction and tilting (28 35 86 87 126 175) Stronger stimuli however do raise the renin level (68 88 137 176) Low renin levels with a diminished response to stimulation have also been found in some normotensive subjects (147) The mechanism of the low renin state has not been elucidated so far Although several possibilities including mineralocorticoid excess volume expan

sion, electrolyte disturbances and reduction in sympathetic activity have been proposed to characterize low renin hypertension as a distinct nosological entity the evidence is far by conclusive.

Renin levels have been described to vary inversely with age in normotensives (1 36 82, 147 160) although this is not a consistent finding (148-150 153 164 167 189 204) In hypertension such a relationship has been found more often (1 11 148 150 160 164 167 189 204) but in some studies this could not be confirmed either (55 98 153 202)
In our cross-sectional study renin levels were also inversely related to age at least below 50 years. On the basis of these observations it can be postulated that the low renin state is a stage in the development of essential hypertension In support of this idea is the negative relationship between renin and blood pressure observed in a number of studies (13 55 112, 115 164 182, 189 193) In other studies, however this relationship was not found (11 24 47 134 153 202). In our study renin was also not clearly related to blood pressure although there was a weak inverse relationship between these variables in the group with intact glomerular filtration rate This suggests some feed-back suppression of renin at higher levels of blood pressure as long as glomerular filtration is intact Since these trends do not reach statistical significance it is probable that blood pressure per se is not the only determinant of renin secretion.
It has been reported that renin levels correlate positively with renal blood flow and inversely with filtration fraction and renal vascular resistance (145 153 163 165) These findings have been interpreted in favour of the baroreceptor theory on renin release. In this large study we failed to observe a relationship between renin and renal blood flow or filtration fraction. However a significant relation was found between renin and renal vascular resistance This may indicate that renin secretion is governed by the combined effect of intravascular pressure and the condition of the renal vasculature In accordance with the baroreceptor theory a rise in blood pressure will suppress renin secretion and this can happen because the pressure is transmitted along the renal vessels (133) However the drop in arterial pressure along the vascular tree in the kidney is dependent on the resistance of the intrarenal vessels Therefore the height of the blood pressure at the level of the juxtaglomerular apparatus does not necessarily reflect the pressure as measured in a peripheral artery
We found that a small rise in renal vascular resistance even when this is still in the normal range influences renin release This was apparent for the cross-sectional as well as the follow-up study Whether this is due to the accompanying reduction in glomerular filtration or to a greater fall in afferent arteriolar pressure cannot be distinguished It is unlikely that the rise in renal vascular resistance is caused by increased renin secretion since these two parameters change in opposite directions in the early stages of hypertension
Apparently beyond a certain age blood pressure is less easily transmitted along the renal vessels which results in more impaired glomerular filtration and consequent stimulation of renin secretion At this stage renin could well be involved in a further increase in renal vascular resistance as may be the case in those patients who exhibited extremely high values for their R.V R
In the patients below the age of 50 years the decline in renin levels could not be related to alterations in blood pressure renal function or volume status. It cannot

vascular resistance (3 64 170 171) *From the work of Folkow (64) it has become* apparent that in established hypertension the architecture of the vascular bed is altered the wall to-lumen ratio is increased *presumably as a consequence of* medial hypertrophy although it cannot be ruled out that the total number of arterioles is reduced as occurs in spontaneous hypertensive rats (95)
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Although the resistance to blood flow in peripheral vascular beds at maximal vasodilatation was *raised in borderline hypertensives thus suggesting structural* changes already to be present (162) the changes in haemodynamics following physical exercise or volume expansion do not provide evidence for a decreased compliance of the vascular system (12)
Both the functional and the structural components of the increase in resistance may be the sequelae of vasoconstrictor stimuli either originating from the tissue (autoregulation) or from increased activity on the part of pressor systems

A functional vasoconstriction has been thought to be the result of auto-regulation of tissue *blood flow in response to an increased cardiac output There are several* objections to this view In the first place time relations do not fit the model Whereas a substantial increase in peripheral resistance in *hypertension takes many* years a firm auto-regulatory control of tissue blood flow occurs much more rapidly in experimental conditions where the ability of the kidney to maintain extracellular fluid homeostasis is interfered with (8 16 29 31 42 57 58 76 78 127 129 205) In essential hypertension no direct information on such a mechanism is available Although it has been suggested that an initial rise in cardiac output is due to an increased venous return (59 190) this certainly is not due to volume expansion since plasma or blood volume in essential hypertension is normal (6 37 43 53 74 80 97 166 194) or even reduced (48 59 96 103 152 155 158 183 185 188 191) *Although* in the present study no comparison with normotensives was *undertaken* the hypertensive group per se failed to show a relationship between cardiac output *or mean arterial pressure and plasma or blood volume*

The most important point against autoregulation is the absence of a substantial increase in cardiac output in the younger age group
Enhanced systemic pressor activity could be based either on the renin-angiotensin system or on the adrenergic system or both Although several studies have established that values for plasma renin activity (or concentration) and aldosterone are within normal limits in most patients with hypertension rather wide ranges are found in these subjects (17 22 23 27 33 38 45 49 60 69 70 75 86 87 109 118 123 126 143 146 181) High renin *levels are found in only a minority of patients* with essential hypertension This already casts some doubt on the assumption that increased activity of *the renin-angiotensin system plays* a role in the rise of vascular resistance Moreover in about one third of patients plasma renin is abnormally low *(for references see 46) In these* cases renin is suppressed and unresponsive to stimuli as sodium restriction and tilting (28 35 86 87 126 175) Stronger stimuli *however* do raise the renin level (68 88 132 176) Low *renin levels* with a diminished response to stimulation have also been found in some *normotensive* subjects (147) The mechanism of the low renin state has not been elucidated so far Although several possibilities *including mineralocorticoid excess* volume expan

Complications of hypertension – myocardial infarction

Myocardial infarction is a well-known complication of essential hypertension and during our follow-up study this event occurred in five patients who were subsequently re-evaluated when they were in a stable condition Although cardiac output and peripheral resistance were not consistently measured in this group the expected changes are a fall in cardiac output and a pronounced rise in vascular resistance (10)

Since myocardial infarction in this study did not influence the blood pressure levels it is likely that the maintenance of arterial pressure was largely based on the increase in total vascular resistance This also bears some consequences for the renal circulation Indeed the complicated group showed a greater absolute fall in renal blood flow and a steeper increase in renal vascular resistance than the uncomplicated group

Since only five patients met with myocardial infarction we were unable to identify these differences as statistically significant.

There were only two factors which discriminated the two follow-up groups at the start of the study age and level of blood pressure. Both were higher in the group which subsequently developed myocardial infarction Of special interest is the observation that in this group renin levels tended to be lower while plasma volume was somewhat higher The concept of Brunner (24) on the protective action of the low renin state although already seriously critisized by others is thus further invalidated.

Comparison of the two follow-up groups give rise to a few more conclusions. When related to age blood pressure in the uncomplicated group is exactly what would have been expected on the basis of the regression line from fig. 3 However in the complicated group blood pressure is much higher than predicted by age alone Whether this inappropriate rise has occurred suddenly or is merely the reflection of a more severe type of hypertension from the onset cannot be determined

After the myocardial event renin levels have increased significantly This phenomenon cannot be attributed to blood pressure per se but again seems to reflect haemodynamic and pressure changes within the kidney

be excluded therefore that the effect of hypertension is superimposed on a physiological reduction in renin secretion

When glomerular filtration rate has fallen below 55 ml/min /m renin is directly related to plasma volume and the quotient P V /I F This reflects the inability of blood pressure to be transmitted throughout the capillary system and explains the positive relation between plasma volume and total peripheral vascular resistance

One could argue that sodium intake could disturb the other relations by influencing renin secretion However all our patients were in sodium balance during the studies They received 60 mmol of sodium a day From the original description of Laragh s group (24) where plasma renin activity is related to urinary excretion of sodium it is apparent that at an excretory level of about 60mmol sodium a good differentiation can be made between low normal and high renin levels It should be borne in mind however that sodium restriction could affect plasma volume more readily in those subjects who exhibit a low renin state Our low sodium intake regime may therefore have disturbed a negative relationship between plasma volume and P R C

An other objection against the results could be that over the years the result of the P R C determination may have been fluctuating We therefore have frequently tested our samples and even checked the relationships for three periods of three years These tests did not reveal any differences in the relationships observed

It has been stated that aldosterone levels are lower in older (normotensive) age groups (36 61) and at higher diastolic pressures (193) Since aldosterone secretion is dependent on several factors including the renin-angiotensin system most studies on this hormone have a dynamic rather than a static character In hypertensive subjects the role of aldosterone production has mainly been investigated in the low renin state In these patients aldosterone secretion and excretion have been reported to be normal and sometimes less responsive than renin (28 30 85 98 113 118 124 135 148 149 166 167 201 203) On the other hand Walker (193) demonstrated suppression of aldosterone at higher levels of blood pressure thus simulating the renin pattern This finding argues against the concept of aldosterone excess in low renin hypertension In our study aldosterone was not related to age blood pressure or P R C It only showed a borderline significant direct relation to extracellular (and interstitial) volume but not to plasma volume

Taking all these observations together it is unlikely that the renin-angiotensin aldosterone system is of primary importance in the elaboration of essential hypertension As soon as substantial vascular alterations occur the system apparently becomes geared into action even before the development of malignant hypertension

Pressor reactions could also be mediated via the alternative pathway the adrenergic system The activity of the adrenergic system is now being assessed by determining the level of circulating catecholamines both in the steady state and during provocative manoeuvres

There is still much controversy at this stage and a primary role of this system in the genesis of essential hypertension remains to be proven

SUMMARY

In this study the results are presented of the haemodynamic and endocrinological inventarisation of 707 patients with essential hypertension. After establishing the relations of the various parameters with age (part IIA) interrelations between these variables are described (part IIB) The general finding is an increase in total peripheral vascular resistance early in the course of essential hypertension In particular this rise in resistance is found in the renal vasculature

In part III emphasis is given to the natural history of essential hypertension on the basis of a follow-up study Again a rise in renal vascular resistance is found
As pointed out in the discussion (part IV) the cause of the abnormal resistance remains unknown. Emphasis is given to the renin-angiotensin system which plays only a minor role Here the factors regulating long-term renin secretion are discussed in favour of the baroreceptor theory

SUMMARY

In this study the results are presented of the haemodynamic and endocrinological inventarisation of 207 patients with essential hypertension. After establishing the relations of the various parameters with age (part IIA) interrelations between these variables are described (part IIB) The general finding is an increase in total peripheral vascular resistance early in the course of essential hypertension In particular this rise in resistance is found in the renal vasculature

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APPENDIX

Table A 1

Individual (raw) data for all 207 patients included in the cross-sectional study

Nr	Sex	Height	Weight	B S A	Age	M A P	Var	C O Dye	C O Imp	T P R	P V
1	M				54	140		6,53		1715	
2	M	173	61,2	173	56	110	26		6,8	1294	2713
3	F	168	70	180	50	122	11	3,76		2596	2450
4	M	166	81	189	66	137			5,9	1858	2839
5	M	173	69	182	39	140			5,1	2196	2619
6	M	179	76	194	37	100	33	5 8		1560	2660
7	M	178	72,5	190	43	125			4,4	2273	2680
8	M	173	74	187	34	105		3 8	4 2	2222	2702
9	F	161	65	168	70	-					
10	F	173	62	174	35		32				2678
11	F	175	79	194	38	116	41	4 7		1870	2895
12	F	175	76	191	42						2636
13	F	175	75	190	45	127			5,1	1992	3257
14	M	176	83,5	199	57	87		4,3	4,0	1619	2154
15	M	184	68,8	190	17	105		8,2		1024	2914
16	M	172	74,4	185	53	163		5,12		2552	
17	M	170	70	181	55						3198
18	M	169	74	184	56	147			4 6	2557	3106
19	M	177	68 8	185	45	140					2748
20	M	172	84	197	55	131	41	7,8		1310	3150
21	F	164	68	174	61	145		4,1		2829	3000
22	M	183	87	210	28	122			7 8	1251	3634
23	F	160	53	154	56	115	32	3,08		2987	2360
24	M	170	64	174	39	113	50	8 1		1150	2745
25	M	181	85 9	206	44	100			5,1	1569	3732
26	M	181	84,9	206	45	100	22		3 6	2222	3430
27	M	165	75 1	182	52	137			4 1	2673	2585
28	M	170	71 2	183	31	115	14		4 6	2000	2571
29	M	178	74	192	41	120		3 96		2424	2274
30	M	176	83 5	200	30	137			5 5	1993	3100
31	M	175,5	82 2	198	36	105	42		5 3	1585	3196
32	F	171	68 1	179	37	110			6 2	1419	2664

B V	E C V	Cyano G F R	Inulin	R P F	R B F	R V R	P F	P R C	P Aldo
3024			103	303	561	15 686	0 34	12 4	10 9
3952		111		407	656	14 878	0 27	2 4	
3357		102	111	453	871	12 583	0 25	14 1	18 8
4762	11 0	76	79	267	485	23 093	0 30	21 3	26 7
4508	15 5	123		677	1167	6 855	0 18	8 0	
5154			120	586	1126	8 880	0 20	8 8	6 4
5004	9 4	120	127	420	778	10 797	0 30	8 6	10 9
		120	110	367	655		0 30	10 5	
4463									
4991	13,0	148		720	1241	7 478	0 21	5 6	
4321	10 2	120		645	1057		0 19	5 4	
5428			147	608	1030	9 864	0 24	4 0	13 7
3916				419	776	8 969		8 3	15 6
5024	10 7	127	121	684	1140	7 368	0 18	15 9	
	12 8							26 6	3 1
5922		114	96	341	631		0 28	16 1	6 7
5860			91	329	621	18 937	0 28	15 9	9 4
4738	7 6	116	113	537	1013	11 056	0 21	9 8	
5250	15 2	130		568	979	10 705	0 23	4 4	
4688	12 7	127		513	916	12 664	0 25	2 8	
6730				707	1309	7 456		7 5	21 7
3471	8,8	96		484	793	11 602	0 20	2 2	
4733				225	409	22 103		16	
6547			146	577	1030	7 767	0 25	8 5	6 3
6236			129	581	1056	7 576	0 22	7 3	11 8
4700				435	806	13 598		4 4	24 3
4944	9 6		99	505	935	9 840	0 20	13 0	6 3
3610			105					9 6	
5849				693	1308	8 379		10 3	8 9
5510			126	483	833	10 084	0 26	7 7	7 4
4298				524	832	10 577		3 4	

Nr	Sex	Height	Weight	BSA	Age	MAP	Var	Dye	CO Imp	TPR	PV
33	F	160	59,8	162	19	123			5,4	1822	2392
34	F	159	57,6	158	54	123			3,9	2523	2162
35	F	162	63 6	168	62	175		3,66		3825	
36	F	164	70	176	44		21				2223
37	F	163	72	176	45	116		3,7		2660	2274
38	F	163	68	174	49	146		4,33		2697	
39	F	164	72,9	179	53	127			7,2	1411	2517
40	M	162	65	169	50	132		4,34		2439	2939
41	F	165	65	171	61	134		8,8	5,7	1218	2336
42	M	180	68,2	186	36						3100
43	M	179,5	70	188	38	103	44		3,49	2361	3095
44	M	180	83	202	37	108					3621
45	F	154	48,8	144	39	139			2,99	3719	2341
46	F	163	53	156	34						2138
47	M	185	87,6	212	41	178		5,88		2422	
48	M	182	74,4	195	60	135	26		5 1	2118	3613
49	M	194	95	226	29	111		7,37		1210	2994
50	F	163	64,9	170	27						2327
51	M	182	76,3	197	27	127		7,2		1411	3288
52	M	182	79,4	200	29	114			5,28	1720	3431
53	F	158	65,2	166	68	183					2439
54	F	158	64	165	69	142			2,82	4028	2730
55	M	182	81	202	41	115	31	7,4		1243	3045
56	M	186	85	210	43						3086
57	M	170	61	170	52	170	16		5 5	2472	3365
58	F	162	57	160	39	140		6		1867	2688
59	F	167	73	182	53	125	42	5,4		1852	2995
60	M	165	79	186	58	145		5,4		2148	2545
61	F	167	81,6	190	56	120		5,3		1811	4755
62	M	172	67,3	179	60	160					2654
63	F	171	64	175	49	120		6 0		1600	
64	M	184	71,5	193	21	95	31		4 2	1810	3

B V	E C	Cyan G I	Inul	R P	R B	R V	F F	P R	P Al
14054		121	108	667	1093	9 003	0 16	4 1	21,6
3664				410	707	13 918		3 7	22 1
	9 9	113		188	308	45 455	0 60	6 4	
3705				361	645			2 5	
3728		108		381	646	14 365	0 28	3 5	
	10 6	110		479	812	14 384	0 23	3 9	
4195				320	525	19 352		1 4	15 4
4453	10 4	87		405	614	17 199	0 21	5 3	
4247				442	804	13 333		12 7	14 6
5741		132	129	608	1086		0 21	14 0	
6448			139	555	1156	7 128	0 25	12 4	9 8
6706	12 3	140	128	575	1065	8 113	0,22	15 0	7,5
4335	9 1		75	313	559	19 893	0,24	12,3	6,3
3341		76	70	295	492		0 24	11 2	
	10 9	120	106	264			0 40	16 8	
6229			102	345	595	18 151	0 30	6 2	5 8
4990	9 8		166	775	1359	6 564	0 21	8 7	
4082								17 4	13 2
5573	13 6		130	980	1849	5 495	0 13	12 2	
5916			141	888	1531	6 108	0 16	11 8	13 7
4435	9,4	91	80	227	420	34 857	0 35	9 1	
4789	10 9		75	200	339	33 510	0 38	20 1	36 9
5342	14 7	143		743	1376	6 686	0 19	5 4	
5321		139		673	1202		0 21	8 3	
5608			123	360	600	22 667	0 34	10 6	31 9
4556		119		547	977	11 464	0 22	8 0	
4680	11 2	142		475	779	12 837	0 30	3 0	
4314	15 2	123		412	736	15 761	0 30	5 3	
6793	19 9							2 5	
4825	9 7	118		431	706	18 130	0 27	7 8	
	14 8	97		333	564	17 021	0 29	21 3	
5795			143	676	1186	6 408	0 21	17 4	9 8

Nr	Sex	Height	Weight	B S A	Age	M A P	Var	Dye	C O Imp	T P R	P V
33	F	160	59,8	162	19	123			5,4	1822	2392
34	F	159	57,6	158	54	123			3,9	2523	2162
35	F	162	63,6	168	62	175		3,66		3825	
36	F	164	70	176	44		21				2223
37	F	163	72	176	45	116		3,7		2660	2274
38	F	163	68	174	49	146		4,33		2697	
39	F	164	72,9	179	53	127			7,2	1411	2517
40	M	162	65	169	50	132		4,34		2439	2939
41	F	165	65	171	61	134		8,8	5,7	1218	2336
42	M	180	68,2	186	36						3100
43	M	179,5	70	188	38	103	44		3 49	2361	3095
44	M	180	83	202	37	108					3621
45	F	154	48,8	144	39	139			2,99	3719	2341
46	F	163	53	156	34						2138
47	M	185	87,6	212	41	178		5,88		2422	
48	M	182	74,4	195	60	135	26		5,1	2118	3613
49	M	194	95	226	29	111		7,37		1210	2994
50	F	163	64,9	170	27						2327
51	M	182	76,3	197	27	127		7,2		1411	3288
52	M	182	79,4	200	29	114			5,28	1720	3431
53	F	158	65,2	166	68	183					2439
54	F	158	64	165	69	142			2,82	4028	2730
55	M	182	81	202	41	115	31	7,4		1243	3045
56	M	186	85	210	43						3086
57	M	170	61	170	52	170	16		5,5	2472	3365
58	F	162	57	160	39	140		6		1867	2688
59	F	167	73	182	53	125	42	5,4		1852	2995
60	M	165	79	186	58	145		5,4		2148	2545
61	F	167	81,6	190	56	120		5 3		1811	4755
62	M	172	67,3	179	60	160					2654
63	F	171	64	175	49	120		6,0		1600	
64	M	184	71,5	193	21	95	31		4,2	1810	3303

I I	B V	E C V	Cyano O F R	Inulin	R P F	R B F	R V R	F F	P R C	P Aldo
3	6414	15 6	110		490	817	15 667	0 22	2 1	
	4750			105	535	892	8 251	0 20	8 3	10 4
					731	1354			15	
			90		757	1402	6 847	0 12	16	
	4214	13 2	112		595	1082	8 946	0 19	12	10 5
	6342	16 9	148		598	1049	7 977	0 25	13	
‹	4292								9 7	
	6453	13 8	134		557	1051	11 418	0 24	7 0	
	6385			128	576	1087	9 568	0,22	5 0	4 7
	7115	12 4	122		660	1082	8 909	0,18	10 2	
	5305			137	568	1014	8 205	0,24	7 9	15 2
	5047	12 2	74	74	189	295		0,39	11 0	
	5243	11 1		63	209	332	35 108	0 30	10 8	11 2
	3077	10 9	107		336	560	20 714	0 32	5 7	
	4611	13,9			507	805	12 522		5 5	
		13 9	124		453	719		0 27	5 0	5 6
	5018	22 4							15 6	69 4
	4523		145	102	391	611	17 610	0 26	14 6	13 8
	4191	9 6	106	98	387	645	15 442	0 25	14 4	
	5026			112	480	842	9 026	0 23	4 3	11 8
	6084				477	782	13 095		3 4	9 0
	5758			160	660	1200	8 600	0 24	15 7	7 5
	6505	9 8	124		559	1055	7 386	0 22	9 1	
	6522	15 9	141	125	513	933	11 790	0 24	9 6	
	5008	16 7	134		709	1289	7 758	0 19	6 1	
	5838		68		573	1042	7 793	0 12	5 5	
	5251			125	561	1020	9 176	0 22	10 0	16 9
	4228			107	333	608	16 132	0 32	9 0	34,2
	4542	10 1		70	353	579	19 952	0 20	8 7	18 3
	4284			103	432	708	12 090	0 24	7 5	7 0
			143		779			0 18	4 3	
	3946			117	667	1112	7 698	0 18	5 4	1 2

Nr	Sex	Height	Weight	BSA	Age	MAP	Var	CO		TPR	PV	[illegible]
								Dye	Imp			
65	M	182	86	207	50	160		5,61		2282	3720	[illegible]
66	M	176	57	170	29	92	30	8,7	8,8	846	2565	[illegible]
67	M	174	76	190	25		43					
68	M	174	78,2	193	26	120		6,0		1600		
69	M	175	80	195	28	121		5,58		1735	2360	[illegible]
70	M	187	90	216	34	104,6		7,15		1170	3615	[illegible]
71	M	178	66,5	183	32	97,3		7,1		1096	2618	[illegible]
72	M	174	90	204	43	150					3420	[illegible]
73	M	174	94	208	47	130			3,9	1507	3384	[illegible]
74	M	182	80	201	21	120,5		6,85		1407	3842	[illegible]
75	M	184	82	205	23	104		3,86	5,2	2155	2971	[illegible]
76	F	175	88,9	204	69						3028	[illegible]
77	F	172	86,6	200	70	145,7			6,33	1841	3198	[illegible]
78	F	154	47,6	143	36	145		5,35		2168	2000	[illegible]
79	F	159	82	184	44	126	28	5,2		1938	2951	[illegible]
80	F	159			44							
81	F	159	83	185	50	118,5		4,26	3,9	2225	3011	[illegible]
82	F	161	72,5	176	73	134,5		4,68		2299	2895	[illegible]
83	F	164	62	167	27	124,5		4,98	6,6	2000	2431	[illegible]
84	M	169	59	167	48	95			2,9	2621	2865	[illegible]
85	M	175	82,4	198	72	128			3,6	2844	3711	[illegible]
86	M	180	81 2	200	26	129			5,28	1955	2994	[illegible]
87	M	172	75	188	39	97,4		6,62		1177	3838	[illegible]
88	M	184	82,5	206	53	137,5		5,05		2178	3783	[illegible]
89	M	176	90	206	35	125	37	7,4		1351	2955	
90	M	176	87	204	37	101,5		6 5		1249	3211	
91	M	176	94	207	41	117			5,8	1613	2888	
92	M	175	68	183	45	122			7,0	1394	2452	
93	F	157	83 2	184	55	144,4		3,62	3,69	3191	2680	
94	F	160	56	157	47	107			4 2	2038	2485	
95	F	165	65,5	172	24							
96	F	165	57	162	29	107			4,0	2140	2407	

B V	E C V	Cyano G F R	Inulin	R P F	R B F	R V R	F F	P R C	P Aldo
6613				608	1067	10 047	-	8,8	
4915	12 7	114		515	888	11 712	0 22	2 5	
4361	10 0	133		671	1137	8 443	0,20	5,3	
4661		85	70	237	389	28 792	0,30	8 1	12 6
		128		387	717	13 389	0,33	3,2	
		141		359	668		0 39	9,1	
4976			82	172	273	42 491	0 48	26,5	24 7
5352	14 1	164		783	1450	6 621	0,21	7 5	
5672	14 6							10 6	
5974			138	892	1538	6 242	0 15	10 9	16 6
5616			114	541	984	9 959	0,21	12 5	6 5
3823	11 1	121	105	540	871	10 608	0 19	8 0	
3321	10 7	107	85	361	547	18 501	0 24	5 5	
6387	10,9		122	555	1009	9 911	0 22	16 9	12 1
4502				499	846	11 537		11 3	7 1
7311	10,9		55	92	146	76 438	0 60	15 2	66 3
5009	9 6							8 6	16 0
3825	9 8	100	99	491	767		0 20	3 5	
	10 6		70	129	215	55 814	0 54	7 8	
3582			53	115	202	65 347	0 46	12 2	39 4
4868	7 9		98	261	458	20 961	0,36	4 1	17 9
3991		65		268	454		0 24		
3531	8 0	98		411	663	15 324	0 24	6 4	
4224			100	487	812	11 881	0 21	7 9	12 7
4491				415	883			10	
4224	12 4	112		355	645	17 364	0 32	4 3	
4074	11 3	115		585	929	8 611	0 20	3 6	
6822				773	1356	7 906			
		167		763	1339		0 22	5 3	
6732			128	540	982	9 939	0 24	13 4	20 4
3448				328	547	16 819		13 3	
		75		229	352		0 33	2 6	

Nr	Sex	Height	Weight	BSA	Age	MAP	Var	Dye	CO Imp	TPR	PV
97	M	182	85,9	207	43	134	34	7,2		1489	3968
98	F	167	74	183	50	130	32	5,07		2051	2900
99	M	174	70	184	31	120	33	7,1		1352	2660
100	F	163	70	175	64	140			5,1	2196	2890
101	M	178	84	202	59	120					
102	M	178	84	202	60						
103	M	167	60	167	58	145			5,5	2109	3334
104	M	186	99	224	45	120		7,8		1231	3104
105	M	183	93	215	47	124		7,73		1283	3290
106	M	183	94,5	216	50	120			7,1	1352	3405
107	M	177	77	194	58	122,5		4,08		2402	3145
108	F	171	68,5	180	25	115,5		4,2		2200	2370
109	F	163	63	168	51	126,5		6,55		1545	2059
110	M	183	85,8	208	43	125			5,7	1754	3385
111	F	171	73,3	185	45	122			5,1	1914	2431
112	M	172	79	192	57	139,5		3,44	4,7	3244	4460
113	M	173	67,5	180	35						2805
114	F	165	55,5	160	30						2295
115	F	156	59	160	50	150		4,46		2691	
116	F	154	63	161	57	165					2042
117	F	160	64,4	167	53	120			4,4	2182	2580
118	F	165	56,3	161	52						2594
119	F	165	57	162	40	127		4,2		2419	2295
120	F	165	55,5	160	45	120			6,1	1574	2492
121	M	163	73	179	52						2111
122	M	162	68	173	55	140	31	3,9		2872	2323
123	F	159	70	172	35	100	43	6,95		1151	2770
124	M	189	85	212	43	134		6,5		1649	4093
125	M	189	84,5	212	44						
126	M	189			50	122			4,2	2324	3568
127	F	161	59,2	162	43	115	34	5,2		1769	2000
128	F	161	59,3	162	43						

B V	E C V	Cyano O F R	Inulin	R P F	R B F	R V R	F F	P R C	P Aldo
6613				608	1067	10 047	-	8 8	
4915	12,7	114		515	888	11 712	0 22	2 5	
4361	10,0	133		671	1137	8 443	0 20	5 3	
4661		85	70	237	389	28 792	0,30	8,1	12,6
		128		387	717	13 389	0 33	3 2	
		141		359	668		0 39	9 1	
4976			82	172	273	42 491	0 48	26 5	24 7
5352	14 1	164		783	1450	6 621	0 21	7 5	
5672	14,6							10 6	
5974			138	892	1538	6 242	0 15	10 9	16 6
5616			114	541	984	9 959	0 21	12 5	6 5
3823	11 1	121	105	540	871	10 608	0 19	8 0	
3321	10 7	107	85	361	547	18 501	0 24	5 5	
6387	10 9		122	555	1009	9 911	0 22	16 9	12 1
4502				499	846	11 537		11 3	7 1
7311	10 9		55	92	146	76 438	0 60	15 2	66 3
5009	9 6							8,6	16 0
3825	9 8	100	99	491	767		0,20	3 5	
	10 6		70	129	215	55 814	0 54	7 8	
3582			53	115	202	65 347	0,46	12 2	39 4
4868	7,9		98	261	458	20 961	0 36	4 1	17 9
3991		65		268	454		0 24		
3531	8 0	98		411	663	15 324	0 24	6,4	
4224			100	487	812	11 881	0 21	7 9	12 7
4491				415	883			10	
4224	12 4	112		355	645	17 364	0 32	4 3	
4074	11 3	115		585	929	8 611	0 20	3 6	
6822				773	1356	7 906			
		167		763	1339		0 22	5 3	
6732			128	540	982	9 939	0 24	13 4	20 4
3448				328	547	16 819		13 3	
		75		229	352		0 33	2 6	

Nr	Sex	Height	Weight	B S A	Age	M A P	C O Var	C O Dye	C O Imp	T P R	P V
97	M	182	85,9	207	43	134	34	7,2		1489	3968
98	F	167	74	183	50	130	32	5,07		2051	2900
99	M	174	70	184	31	120	33	7,1		1352	2660
100	F	163	70	175	64	140			5,1	2196	2890
101	M	178	84	202	59	120					
102	M	178	84	202	60						
103	M	167	60	167	58	145			5,5	2109	3334
104	M	186	99	224	45	120		7,8		1231	3104
105	M	183	93	215	47	124		7,73		1283	3290
106	M	183	94,5	216	50	120			7,1	1352	3405
107	M	177	77	194	58	122,5		4,08		2402	3145
108	F	171	68,5	180	25	115,5		4,2		2200	2370
109	F	163	63	168	51	126,5		6,55		1545	2059
110	M	183	85,8	208	43	125			5,7	1754	3385
111	F	171	73,3	185	45	122			5,1	1914	2431
112	M	172	79	192	57	139,5		3,44	4,7	3244	4460
113	M	173	67,5	180	35						2805
114	F	165	55,5	160	30						2295
115	F	156	59	160	50	150		4,46		2691	
116	F	154	63	161	57	165					2042
117	F	160	64,4	167	53	120			4,4	2182	2580
118	F	165	56,3	161	52						2594
119	F	165	57	162	40	127		4,2		2419	2295
120	F	165	55,5	160	45	120			6,1	1574	2492
121	M	163	73	179	52						2111
122	M	162	68	173	55	140	31	3,9		2872	2323
123	F	159	70	172	35	100	43	6,95		1151	2770
124	M	189	85	212	43	134		6 5		1649	4093
125	M	189	84,5	212	44						
126	M	189			50	122			4,2	2324	3568
127	F	161	59,2	162	43	115	34	5,2		1769	2000
128	F	161	59,3	162	43						

B V	E C V	Cyano G F R	Inulin	R P F	R B F	R V R	F F	P R C	P Aldo
	10 3							17 2	
39259		72	81	289	535	23 028	0 28	15 9	12 8
4216	11 9	99	127	329	621		0,39	8 1	
4818	13 9	155		1023	1764	4 762	0 15	8	
5587			101	339	605	18 282	0 30	15 8	15 0
3834	7 4							20 8	
4826	10 8		165	528	866	12 776	0 31	14 1	6 9
4504			100	549	980	9 796	0 18	11 4	5 1
		82		308	550		0 27	40	
5395	12 6	107	118	493	836		0 24	7 8	
		152	115	559	1016		0 21	22 2	
3379	9 4		86	209	299	36 120	0 41	6 8	7 3
5343				241	389				
4956			114	492	863	12 051	0 23	22 4	33 8
3686			106	539	914	10 066	0 20	8 3	12 2
5117	10 8	165		773	1487	5 649	0 21	6 7	
4361	7 0							3 8	
3162			87	479	785	10 191	0 18	15 2	10 1
4925				619	1263	7 918		12	
	14 8	125		425	708	19 774	0 29	1 8	
5045			62	205	347	31 170	0 30	11 8	5 1
4510			105	440	710	11 493	0 24	5 7	43 7
4919				847	1366	6 676			
4583	12 8	154		828	1355	9 588	0 19	5 0	
5100	9 5	118		458	777	10 656	0 26	9 7	43 1
4915	13 5	185		599	1175		0 31	9 8	
3932								15 8	
4792			106	368	566	20 071	0 29	6 6	44 9
3567		94	92	425	733	12 715	0 22	3 6	10 6
3456	14 5	166	113	567	930	13 763	0 20	3 6	
3495	8 9	66	87	440	733	11 405	0 20	13 2	

Nr	Sex	Height	Weight	BSA	Age	MAP	Var	Dye	CO Imp	TPR	PV
129	M	164			34	131,5		7,55		1393	
130	F	161	60	163	50	154		3,47	5,43	3550	5000
131	M	172	74	187	63						2108
132	M	180	74	193	24	105	50	9,1		923	
133	M	179	75	193	24	105		7,6		1105	3180
134	M	173	75,8	189	58	121			5,1	2115	3073
135	F	168	62	170	31	124,3		5,28		1883	2684
136	F	168	63,4	172	34	138,3		4,82	5,64	2295	2944
137	M	167	64	172	18	120	26		7,3	1315	2432
138	F	163	63,4	168	64						
139	M	186	79,3	203	30						2967
140	M	186	87	212	64						
141	F	156	55	154	52	135			4,1	2634	2298
142	F	171	60,5	170	47						3473
143	F	164	56	160	44	130			5,3	1962	2825
144	F	150	56	151	36	115			4,9	1877	2175
145	M	183	82,3	204	28	105	37	7,8		1077	3070
146	F	163	47	148	50	158		2,62		4824	2442
147	M	155	57	155	58	100	16		3,0	2667	1929
148	M	158	68	170	53	125	37	6,3		1587	2758
149	M	181	82,7	203	63	175	12	5,85		2393	
150	F	164	60,7	165	57	135,2			4,18	2588	2674
151	F	152	61 5	158	58	102					2751
152	F	165	60	166	28	114	48	7,6		1200	3148
153	F	174	71	185	44	160	30	7 85		1631	2933
154	M	180	75	194	36	103,5		7 9		1048	2805
155	M	171	91,8	204	43						2605
156	F	161	60 3	163	47	131		3,48		3011	2359
157	F	166	69,5	177	46	142			4,2	2705	3163
158	F	155	51	148	47	116 5		3 66	3,7	2546	2069
159	M	180	88	208	60	160					2177
160	M	168	51	157	24	104,5		5 92		1412	1957

B V	E C V	Cyano G F R	Inulin	R P F	R B F	R V R	F F	P R C	P Aldo
		160		608	1105		0 26	5 8	23 3
4359		105		653	1146	5 585	0,16	5 5	
6678	15,7	175		627	1140	8 421	0,28	3 4	
6820	12 5	155		632	1170	8 547	0 25	6 4	
6206								23	
4215				633	1055			14 9	
4256			108	455	784	15 306	0 24	2 2	18 5
5665			122	500	926	8 639	0 24	8,7	14 8
4790								17 1	
4786	7 4	117	116	521	883	9 875	0 22	11 6	18,2
5305	12 6	125		577	1089	9 550	0 22	5 3	
4852									
4784		134		465	861	12 544	0 29	2 4	
		117	110	455	812		0 24	8 6	
5675	8 6	125	118	376	684	15 883	0 31	8 6	21 4
4202	8 7							22 6	
4098	8 9	88	75	305	555	22 342	0 25	5 8	
4716				427	712	13 034		2 3	8 4
4300	10 2	93		351	585	17 915	0 26	8 0	
2825	9 8	95		484	849	12 250	0 20	5 3	
6758	10 5	146	158	420	712	13 371	0 35	8 6	
3702	9 6	93	74	363	648	19 753	0 20	3 6	
4271	7 7		64	307	512	19 656	0 21	8 6	30 8
5272			110	312	578	16 609	0 35	9 7	21 5
5095	16 5	155		593	1059	10 576	0 26	5 4	
5515	12 8	135		449	748	13 829	0 30	2 3	
5537	12 9	108		463	874	12 082	0 23	10 0	
6528		132	135	339	556	21 367	0 40	5 6	2 1
3560	9 3	86	80	396	660	13 939	0 20	7 4	
4356			101	444	783	12 218	0 23	9 3	8 0
5333	16 2		127	587	962	14 012	0 22	9 0	15 2
5929	13 9	151		456	894	11 544	0 33	11 1	

Nr	Sex	Height	Weight	B S A	Age	M A P	Var	C O Dye	C O Imp	T P R	P V
161	M	184	104	227	53						
162	M	162	65	169	35	80	38	6,62		967	2790
163	M	179	84	202	54	120		5,2		1846	3940
164	M	179	81,5	200	55	125		6,4		1562	3751
165	M	178	84,1	202	56						3289
166	F	167	70	178	53						2571
167	F	163	58,6	162	50	150	22		5,0	2400	2290
168	M	179	83,4	202	49	100	28		3,7	2162	3229
169	F	158	63	164	70						2874
170	M	171	78,5	191	43	109		4,79		1820	2680
171	M	182	74	195	23	130	46	5,8		1793	2918
172	M	174	69,5	183	54						2911
173	M	172	67,5	180	55	135	31	5,85		1846	2918
174	M	173	75	189	59						
175	F	160	56,8	158	41	135,8		4,29	5,7	2532	2894
176	M	161	63	166	51						2395
177	M	156	60,4	160	58	155					2254
178	F	163	64	169	47	116	28	4,6		2017	2924
179	F	162	65,8	170	49	131					2752
180	F	163	60	164	23	130	29	4,3		2419	1780
181	M	186	82	206	45	119		6,87		1386	4055
182	F	159	52	152	30	160		4,6		2783	2184
183	F	166	65,7	173	57	125,8		5 13	4,1	1962	2349
184	M	168	70	179	70	120		5,35	5,1	1794	2847
185	M	183	60	208	60	140	40	7,1		1577	2955
186	M	183	63	200	63	129,3		4,71		2196	3309
187	M	184	64	204	64	132		5,99		1763	2990
188	M	183	66	206	66	148,5		4,04		2941	3917
189	F	162	22	152	22	115					2207
190	F	162	24	157	24	115			4,6	2000	2483
191	F	163	53	190	53	168,5	18		3,7	3643	3093
192	M	182	55	226	55	129		3,62		2851	3083

B V	B C V	Cyano G F R	Inulin	R P F	R B F	R V R	F F	P R C	P Aldo
		160		608	1105		0 26	5 8	23 3
4359		105		653	1146	5 585	0 16	5 5	
6678	15 7	175		627	1140	8 421	0,28	3 4	
6820	12,5	155		632	1170	8 547	0 25	6 4	
6206								23	
4215				633	1055			14 9	
4256			108	455	784	15 306	0 24	2 2	18 5
5665			122	500	926	8 639	0 24	8 7	14 8
4790								17 1	
4786	7 4	117	116	521	883	9 875	0 22	11 6	18 2
5305	12 6	125		577	1089	9 550	0 22	5 3	
4852									
4784		134		465	861	12 544	0,29	2 4	
		117	110	455	812		0 24	8 6	
5675	8,6	125	118	376	684	15 883	0 31	8 6	21 4
4202	8 7							22 6	
4098	8 9	88	75	305	555	22 342	0 25	5 8	
4716				427	712	13 034		2 3	8 4
4300	10 2	93		351	585	17 915	0 26	8 0	
2825	9 8	95		484	849	12 250	0 20	5 3	
6758	10 5	146	158	420	712	13 371	0 35	8 6	
3702	9 6	93	74	363	648	19 753	0 20	3 6	
4271	7 7		64	307	512	19 656	0 21	8 6	30,8
5272			110	312	578	16 609	0 35	9 7	21 5
5095	16 5	155		593	1059	10 576	0 26	5 4	
5515	12 8	135		449	748	13 829	0 30	2 3	
5537	12 9	108		463	874	12 082	0 23	10 0	
6528		132	135	339	556	21 367	0 40	5 6	2 1
3560	9 3	86	80	396	660	13 939	0 20	7 4	
4356			101	444	783	12 218	0 23	9 3	8 0
5333	16 2		127	587	962	14 012	0 22	9 0	15 2
5929	13 9	151		456	894	11 544	0 33	11 1	

Nr	Sex	Height	Weight	B S A	Age	M A P	Var	C O Dye	C O Imp	T P R	P V
161	M	184	104	227	53						
162	M	162	65	169	35	80	38	6,62		967	2790
163	M	179	84	202	54	120		5,2		1846	3940
164	M	179	81,5	200	55	125		6,4		1562	3751
165	M	178	84,1	202	56						3289
166	F	167	70	178	53						2571
167	F	163	58,6	162	50	150	22		5,0	2400	2290
168	M	179	83,4	202	49	100	28		3,7	2162	3229
169	F	158	63	164	70						2874
170	M	171	78,5	191	43	109		4,79		1820	2680
171	M	182	74	195	23	130	46	5,8		1793	2918
172	M	174	69,5	183	54						2911
173	M	172	67,5	180	55	135	31	5 85		1846	2918
174	M	173	75	189	59						
175	F	160	56,8	158	41	135,8		4,29	5,7	2532	2894
176	M	161	63	166	51						2395
177	M	156	60,4	160	58	155					2254
178	F	163	64	169	47	116	28	4,6		2017	2924
179	F	162	65,8	170	49	131					2752
180	F	163	60	164	23	130	29	4,3		2419	1780
181	M	186	82	206	45	119		6,87		1386	4055
182	F	159	52	152	30	160		4,6		2783	2184
183	F	166	65,7	173	57	125,8		5,13	4,1	1962	2349
184	M	168	70	179	70	120		5,35	5,1	1794	2847
185	M	183	60	208	60	140	40	7,1		1577	2955
186	M	183	63	200	63	129,3		4,71		2196	3309
187	M	184	64	204	64	132		5,99		1763	2990
188	M	183	66	206	66	148,5		4 04		2941	3917
189	F	162	22	152	22	115					2207
190	F	162	24	157	24	115			4,6	2000	2483
191	F	163	53	190	53	168,5	18		3,7	3643	3093
192	M	182	55	226	55	129		3,62		2851	3083

B V	E C V	Cyano O F R	Inulin	R P F	R B F	R V R	F F	P R C	P Aldo
5323									
		110		436	838	10 979	0 25	12 6	
5002			142	607	1104	7 971	0 23	9 5	1 9
5573	8 7		90	352	618	16 828	0 26	13 6	10 3
6415	12 3		110	427	854	12 178	0 26	3 6	
6743			116	433	787	12 198	0 27	7 0	3 4
5438			156	580	1094	8 775	0 27	4 2	8 6
5530	12 1							6 1	11 7
5221		133		752	1367	6 000	0 18	8	
4540			102	301	528	20 000	0 34	2 0	
5392			101	423	769	12 484	0 24	13 9	6 3
3085	9 6	85		371	580	16 000	0 23	6 1	8 5
3984		124		600	952	12 605	0 21	3 1	
5140			114	368	634	14 132	0 31	8 9	18 5

Nr	Sex	Height	Weight	BSA	Age	MAP	Var	CO Dye	CO Imp	TPR	PV
193	M	172	31	193	31		24				2981
194	M	174	33	195	33	143		7,0		1634	
195	M	173	35	200	35	115		4,6		2000	
196	M	174	40	204	40	110			4,6	1913	2851
197	M	179	73	181	73	130			5,8	1793	2842
198	M	177	45	195	45	130					3336
199	M	177	47	184	47	120	22		4,2	2286	3641
200	M	172	47	196	47	120			6,0	1600	3263
201	M	176	54	191	54	138,5		5,08		2181	3152
202	M	194	25	228	25	117,9		5,93		1591	2924
203	F	160	69	174	69	132			4,8	2200	2588
204	M	174	50	184	50	120			5,4	1778	2804
205	F	156	36	151	36	116	34	5,3		1751	2067
206	F	157	50	154	50	150	29	4,82		2490	2510
207	M	163	58	178	58	112	28				2930

B V	B C V	Cyano G F R	Inulin	R P F	R B F	R V R	F F	P R C	P Aldo
5323									
		110		436	838	10 979	0 25	12 6	
5002			142	607	1104	7 971	0 23	9 5	1 9
5573	8 7		90	352	618	16 828	0 26	13 6	10 3
6415	12 3		110	427	854	12 178	0 26	3 6	
6743			116	433	787	12 198	0 27	7 0	3 4
5438			156	580	1094	8 775	0 27	4 2	8 6
5530	12 1							6 1	11 7
5221		133		752	1367	6 000	0 18	8	
4540			102	301	528	20 000	0 34	2 0	
5392			101	423	769	12 484	0 24	13 9	6 3
3085	9 6	85		371	580	16 000	0 23	6 1	8 5
3984		124		600	952	12 605	0 21	3 1	
5140			114	368	634	14 132	0 31	8 9	18 5

Table A 2.

Individual data presented per m2 for 26 patients with uncomplicated essential hypertension during follow-up

Haemodynamic data of uncomplicated hypertension during the follow-up study

Study	Age	Sex	MAP mm Hg	PV ml/m	RPF ml/min/m²	RVR dyn sec cm⁻⁵/m²	PRC ng/ml hr
INITIAL	_5	M	110	–	514	10263	
FINAL	79.5		91	1509	314	14003	8 3
INITIAL	77	M	125	1661	434	11979	13 7
FINAL	30		117	1707	447	1_294	11 7
INITIAL	31 4	F	130	1646	299	1881	8 8
FINAL	35		128	174	223	28090	11 6
INITIAL	31.5	F	113	1317	3 1	15661	6.9
FINAL	37		114	1508	776	14847	11 1
INITIAL	35	M	117	1449	355	1466_	7 6
FINAL	4		11	1311	765	17574	10 0
INITIAL	36	M	94	1658	378	12839	13 6
FINAL	38		99	1638	785	13373	1 3
INITIAL	37	M	100	1371	349	1 435	7 0
FINAL	43		104	1411	310	14799	7 3
INITIAL	39	F	110	1497	366	14173	5 1
SECOND	4		126	1380	341	18108	7 3
FINAL	45 5		176	1714	319	18804	3 4
INITIAL	40 7	F	131	1408	_57	4579	6 8
FINAL	45 3		131	1558	304	20431	7 8
INITIAL	44	F	148	1604	275	36798	5 5
FINAL	50 6		140	1619	159	44176	13
INITIAL	44	F	135	1285	184	37196	
SECOND	5		139	1363	20_	31284	4 9
FINAL	53.5		176	1406	177	34360	1 4
INITIAL	44	M	130	1676	277	30193	8 4
FINAL	47		138	1643	280	1016	4 9

Haemodynamic data of uncomplicated essential hypertension during the follow-up study

Study	Age	Sex	MAP mm Hg	PV ml/m²	RPF ml/min/m²	RVR dyn sec. cm⁻⁵/m	PRC ng/ml hr
INITIAL	45.8	M	120	1513	337	19044	4.2
FINAL	47.3		130	1502	287	[illegible]291	9.3
INITIAL	44.6	M	153	1940	337	1031	5.9
FINAL	50.5		148	1691	[illegible]46	26184	11.8
INITIAL	45.5	M	100	1980	311	15669	7.5
FINAL	48		113	1586	281	18346	5.9
INITIAL	45.8	M	135	1711	46	1933	2.6
FINAL	47.8		135	1979	229	25404	5.4
INITIAL	47.7	F	170	1740	253	[illegible]561	3
FINAL	53		136	1796	21	34000	4.5
INITIAL	58.3	M	121	1808	179	31632	7.4
FINAL	59.4		177	1746	153	37896	5.0
INITIAL	1	F	170	1487	81	56998	9.3
FINAL	58		166	1268	70	66314	11
INITIAL	3	M	145	1179	[illegible]31	1682	10
FINAL	55		170	1335	220	[illegible]091	9
INITIAL	60.7	M	125		786	79107	5.2
SECOND	63		120	1489	283	30634	1.6
THIRD	64		1 3	1407	229	22743	10.9
FINAL	66.1		145	1618	190	34477	12.5

Table A 3

Individual data for 5 patients during follow-up in whom the course was complicated by myocardial infarction.

Acta Medica Scandinavica

Supplementum 623

New aids in diagnosing acute myocardial infarction

Edited by Bengt W Johansson

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Malmö 1978

CONTENTS

GENERAL LECTURES

FREE LECTURES

Printed in Sweden
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Malmö Centraltryckeri
Malmö 1978

INTRODUCTION

The diagnosis of acute myocardial infarction is based on the patient history electrocardiographic finding, serum enzymes, and the finding of a necrotic myocardium at autopsy For it to be reliable, one or more of these criteria are needed. Early diagnosis is important for several reasons. Most arrhythmic complications appear during the early stage of the infarction. The earlier the diagnosis, the earlier the monitoring can begin. Experimental data indicate that infarct size can be reduced by mechanical assistance or pharmacological interventions. It is not certain that these experimental data can be transferred to clinical practice, but early intervention is essential for a successful result. Early exclusion of acute infarction will save expensive hospital beds.

In recent years, new aids for diagnosing acute myocardial infarction have appeared ST mapping, isoenzymes, radionuclides, determination of myoglobin in urine and serum, and staining and chemical procedures applied to autopsy material. These new aids were a major topic at the Nordic Congress of Cardiology Ystad Sweden, August 26—27 1977 Introductory reviews of them were presented. Voluntary papers, directly relevant, were selected. These are published in the present volume, as is also the closing panel discussion, which sought to adapt these new aids to clinical practice, based on our present knowledge.

I gratefully acknowledge the generosity of the sponsors for making this publication possible

Bengt W Johansson
Heart Section
General Hospital
MALMÖ SWEDEN

PANEL DISCUSSION

INTRODUCTION

The diagnosis of acute myocardial infarction is based on the patient history electrocardiographic finding, serum enzymes, and the finding of a necrotic myocardium at autopsy For it to be reliable, one or more of these criteria are needed. Early diagnosis is important for several reasons. Most arrhythmic complications appear during the early stage of the infarction. The earlier the diagnosis, the earlier the monitoring can begin. Experimental data indicate that infarct size can be reduced by mechanical assistance or pharmacological inter ventions. It is not certain that these experimental data can be transferred to clinical practice but early intervention is essential for a successful result. Early exclusion of acute infarction will save expensive hospital beds.

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MALMÖ SWEDEN

Electrocardiographic mapping of ischaemic myocardial insult

John K Kjekshus

University of Oslo Dept. of Medicine B Rikshospitalet, OSLO NORWAY

Recent research has bown that the extent of myocardial infarction is not determined at the onset of the coronary occlusion. A varying lapse of time takes place before irreversible damage is established. During thi period of reversible myocardial injury some appropriate interventions can f vourably influence the final outcome of the p thological process (1). Because the prognosis of the myocardial insult is dependent on the size of the infarct (2), the testing of thera peutical approaches designed to reduce infarct size ha become a major challenge for linicians. The ischaemic injury is liable to extension as w ll as reduction in the revers ible period dependent on various interacting haemodynamic and metabolic factors that w ll modify the effect of interventions. For instance a decrease in myocardial oxygen requirement obtained by reduction of after load might also res lt in reduction of coronary perfusion pressure and increase in heart rat The resultant effect on the ischaemic rea could therefore be unpredictable Method for qua titating infarct size e onsequently indispensable in the tre tment of p tients with acute ischaemic insult of the myocardium. Current techniques in use for measuring the ischaemic injury include

1) grading of he ischaemic pain (3)
2) nalysis of cumulated creatine kinase (CK) time-acti ity curves (4 5)
3) adionuclide imaging (6)
4) anaerobic metabolites in coronary sinus (7)
5) precordial ST-segment mapping (8)
6) precordial QR-mapping (9)

The use of the electrocardiogram for infarct sizing has obvious advantages It is direct, simple, inexpensi e, and non-inva si e.

Animal experiments

ST-segment elevation

The relation between ST-segment elevation and coronary occlusion was probably first recognized in 1920 (10) Later Raab (11) demonstrated that epicardial ST-segment changes during coronary constriction were augmented by catecholamine stimulation of the myocard um. Experiments initiated in San Diego by Maroko et al. (1) showed that epicardial mapping of ST-segment changes was quite usef l for indexing acute ischaemic injury of the myocardium underlying the exploring electrode (Fig. 1) W thin 30 se conds after coronary artery occlusion, ST segment elevation appears in the area of ischaemia indicated by cyanosis and systolic bulging. Areas outside the ischaemic zone do not show ST-segment elevation. Accordingly the size of the acute ischaemic region can be outlined by the number of epicardial positions displ ying elevations The height of the elev tion wa taken t indicate the magnitude of ischaemic injury and the

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Recent esearch has hown that the extent of myocardial infarction is not determined at the onset of the coronary occlusion A vary ing lapse of time takes place before irrever ible damage n established. During this period of reversible myocardial injury some appropriate interventions can f vourably influence the final outcome of the pathological process (1) Because the prognosis of the myocardial insult is dependent on the size of the infarct (2), the testing of therapeutical approaches designed to reduce infarct size has become a major challenge for clinicians. The ischaemic injury is liable to extension w ll reduction in the reversible period dependent on various interacting haemodynamic and metabolic factors that will modify the effect of interventions. For instanc decre se in myocardial oxygen requirement obtained by reduction of after load might also result in reduction of coronary perfusion pressur and increase in heart ra e The resultant effect on the ischaemic rea could therefore be unpredictable. Method for quantitating inf rct siz ar consequently indispensable in the treatment of p tients with acute schaemic insult of he myocard um. Current techniques in use for ses ing the ischaemic injury include-

1) grading of the schaemic pain (3)
2) nalysi of cumulated creatine kinase (CK) time-act vity curves (4 5)
3) adrenuclide imaging (6)
4) anaerobic metabolites in coronary sinus (7)
5) precordial ST-segment mapping (8)
6) precordial QR-mapping (9)

The use of the electrocardiogram for infarct sizing has obvious advantages: it is direct, simple, inexpens e, and non-invasi e.

Animal experiments

ST-segment elevation

The relation between ST-segment elevation and coronary occlusion was probably first recognized in 1920 (10) Later Raab (11) demonstrated that epicardial ST-segment changes d ring coronary constriction were augmented by catecholamine stimulation of the myocardium. Experiments initiated in San Diego by Maroko et al. (1) showed that epicardial mapping of ST-segment changes was quite useful for indexing acute schaemic injury of the myocardium underlying the exploring electrode (Fig. 1) Within 0 seconds after coronary artery occlusion, ST segment elevation appears n the area of ischaemia indicated by cyanosis and systolic bulging. Areas outs de the ischaemic zone do not show ST-segment elevation. Accordingly the size of the acute ischaemic region can be outlined by the number of epicardial positions displayin levations. The he ht of the levation wa taken to indicate the magnitude of ischaemic injury and the

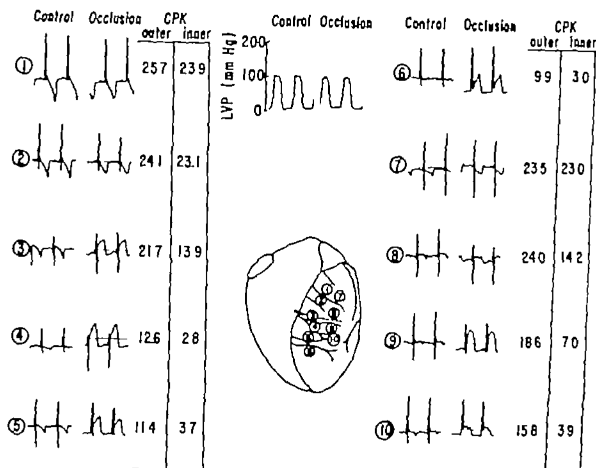


Fig 1 Mapping of epicardial ST-segment changes before and 15 min after coronary occlusion and creatine kinase (CK) activity 24 h later in corresponding subepicardial and subendocardial samples from a representative dog heart. LVP = left ventricular pressure. Locations of numbered sample sites and the occlusive coronary tie are indicated on the central diagram.

number of locations with ST-segment elevation to indicate the extent of the ischaemic area. The ischaemic changes in the ECG was transitory when the coronary occlusion was released *within 20 minutes*. Although the ST-segment changes in each position varied with time they were highly reproducible during repeated occlusions (1) The mapping of epicardial ST-segment elevations therefore provided a tool to study the effects on the ischaemic injury potentials of interventions applied between two subsequent occlusions *of 15 minutes duration*.

Several lines of evidence have been provided in support of the use of ST-segment elevation as a semi-quantitative index of myocardial ischaemic injury ST-segment elevations recorded by intramyocardial electrodes were closely related to reductions in intramyocardial oxygen tension (12) The magnitude of early elevation of epicardial ST segment *in any given position correlated* closely to the metabolic changes in the subjacent myocardium, as evidenced by lactate accumulation and by depletion of ATP and CK (13). ST-segment elevation also corresponded to regional accumulation of hydrogen ions and increase in CO_2 tension (12) Moreover the magnitude of early elevations *of ST-segments in any given* epicardial position presaged the ultimate extent of necrosis indicated by the depression of myocardial CK activity and by morphological evidence of cell death in subjacent

myocardial biopsies taken 24 hours after the coronary occlusion (Fig. 1) (1 14 15 16)

However there are limitations to the use of ST-segment changes as a quantitative index of myocardial injury Although ST segment elevation was closely related to the myocardial injury as measured by regional CK depletion, the magnitude of epicardial ST-segment elevation was inversely related to the distance from the exploring electrode to the local injury ST-segment elevation often did not occur when the myocardial injury was limited to subendocardial regions (15) (Fig. 2) A close relation was observed between ST-segment changes 15 minutes post occlusion and regional blood flow to the subepicardial region of the sampling site determined 24 hours later during microsphere injection (15) There was less ST-segment elevation for reductions in subendocardial blood

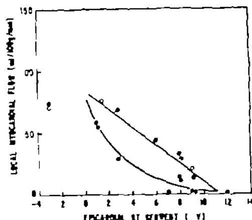


Fig 3. Relation between picardial ST-segments 15 min after coronary artery occlusion and regional blood flow in corresponding subepicardial (0) and subendocardial ( ) regions 24 h later. The curves represent best fits obtained by least squares method. Regional flow was obtained by labelled microsphere technique

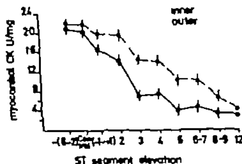


Fig 2 Epicardial ST-segment changes and CK activity in homogenates from outer (0) and inner (I) regions f left ventricle Epicardial ST segment change were recorded 15 min fter coronary artery ligation from non-ischaemic and ischaemic areas Whole wall biopsies from similar sites were taken 24 h later and divided into outer (subepicardial and inner (subendocardial) portions.

flow fitting a non-linear rel tion (Fig.3) This might explain why a less obvious relation wa obtained in other studies that used microsphere determination of flow in the immed'ate post-occlusive period (17 18).

Regional flow in the ischaemic area is highly scattered, and unless small biopsies are taken, spurious results could be obtained. Lek en et al. (19) applied intramyocardial platinum electrodes for ST-segment analysis and local flow determinations with hydrogen desaturations and compared local intra myocardial ST-elevation to local flow Diminutions in flow were found to exceed 30—40 / before ST-segment changes were observed, but were correlated closely with further reduction i flow ST-segment elevation is therefore related to reduction in myocardial ischaemia, but epicardial ST segment changes are less sensiti than those recorded from intramyocardial sites.

The ischaemia causes a reduction the resting membrane potential and a shortening of the action potential. Thus an instantaneous potential difference is set up across the border between normal and abnormal polarized cells causing current flow long as the cell remain electrically coupled. Because shifts are caused simultaneously in resting and active membrane potential, changes

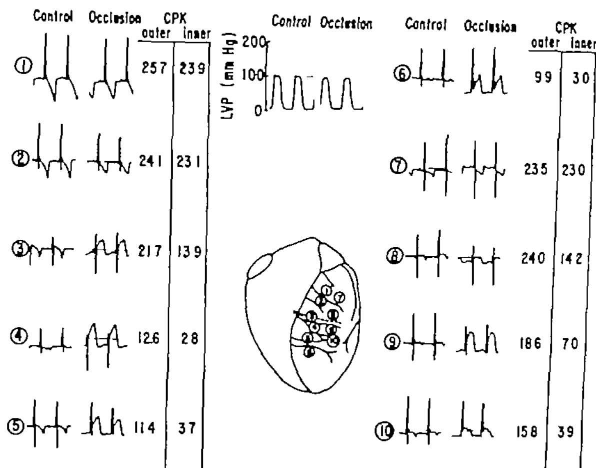


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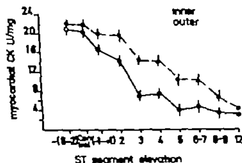


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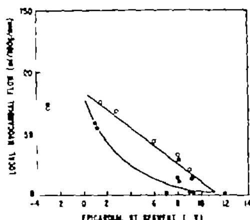


Fig. 3 Relation between epicardial ST-segments 15 min after coronary artery occlusion and regional blood flow in corresponding subepicardial (O) and subendocardial ( ) regions 24 h later. The curves represent best fits obtained by least squares method. Regional flow was obtained by labelled microsphere technique

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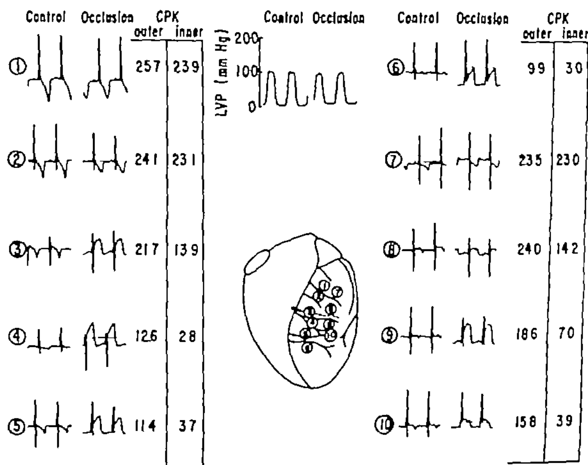


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only ST-segment elevation in the first 15 minutes after coronary occlusion should be used for quantitative evaluation.

When due respect is given to the limits of the method, the close relation between early ST-segment elevation and ultimate extent of regional cell death, strongly qualifies the use of ST-segment elevation for indexing the ischaemic injury. The effect of interventions can therefore be studied by relating the ST-segment elevation obtained 15 minutes after coronary occlusion, before any intervention to the extent of necrosis 24 hours later as reflected in subjacent myocardial CK depression (1 14 15 16). The effect of intervention is evaluated by comparing treated and non-treated groups (Fig 4).

Thus, epicardial ST-segment mapping has proved to be a reliable index of myocardial ischaemia and has been extensively used to test interventions that might reduce or increase the ischaemic injury (1 14 16, 24).

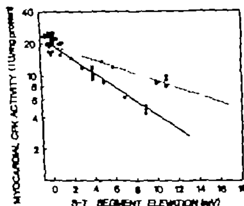


Fig 4 Depression of myocardial CK activity after administration of β pyridylcarbinol in animals with coronary artery occlusions Epicardial recordings were obtained 15 min after coronary artery occlusion from anatomically identifiable sites The artery was then released and permanently ligated CK activity expressed on a logarithmic scale was measured in homogenates from full-wall specimens obtained from the same sites 24 h later Data from animals receiving β-pyridyl-carbinol for 24 h (open circles) and from free untreated animals (closed circles). Solid line represents line for control study (log CK = 1 300—0 067 ST r = 0 89) Dotted line regression line relating ST-segment elevation after coronary artery occlusion before administration of β-pyridyl-carbinol and log CK from corresponding sites 24 h later (log CK = 1.278 —0 033 ST r = 0 78). Animals receiving β-pyridyl-carbinol showed less depression of myocardial CK activity than would have been expected from ST-segment elevation occurring before drug administration (P<0 001)

ST-segment depression

Epicardial ST-segment depression is inconsistently observed at the outer margin of an ischaemic area. In areas with ST-segment depression, the resting and action membrane potentials are increased in contrast to opposite findings in regions with ST-segment elevation.

In most instances, it appears that epicardial ST-segment depression is a primary effect due to the hyperpolarization of the myocardial cell membrane (25) rather than a reciprocal effect of ST-segment elevation in the subendocardial regions, as previously suggested.

ST-segment depression is not associated with evolution of necrosis in any regions of the wall, and subjacent myocardial blood flow is not decreased (15) (Fig. and 3). It follows that during acute coronary occlusion epicardial ST-segment depression has no prognostic significance on the evolution of necrosis.

QRS-changes

Transformation of the ischaemic myocardial cell into an irreversibl damaged cell is reflected in reduction of the height of ST segment elevation The point of no-return, however is associated with conformational changes in the QRS complex appearing 30—45 minutes after the onset of ischaemia. These changes are reflected in the development of Q waves and the reduction of R waves in the immediate overlying epicardium (9). Similar changes are produced im-

will appear in both TQ- and ST-segments (20)

Currently used electrocardiographs are equipped with base-line compensation and do not discriminate between TQ depression and ST-elevation. The recorded ST-segment elevation is actually the sum of the two events (20) Interventions that alter either two will therefore interfere with the recorded ST segment elevation. The ischaemic injury however is always accompanied by true ST-segment elevation and by TQ segment depression, the latter probably being more important (21) But spurious results can be anticipated if an intervention affects selective ST or TQ segment shifts unrelated to the ischaemia.

The changes in resting and active membrane potential and consequently TQ-ST segment shifts are closely related to changes in ion transport and concentration gradients across the myocardial cell membrane. An ionic pump secures intracellular concentrations low in sodium and high in potassium. During ischaemia, the transmembraneous ion gradient is rapidly reduced, because the ionic pump is oxygen dependent and because accumulated potassium is not washed away Regional coronary arterial perfusion with solution of high potassium concentration mimic local ST-segment elevation in the perfused area (22) Conversely washout of extracellular potassium in the ischaemic area reduces ST segment elevation. Spurious changes in the TQ-ST shift might occur with interventions which interfere with the ionic pump such as digitalis, quinidine, and by sympathetic stimulation. Regional differences in intramyocardial conduction velocity induced by the ischaemia, temperature changes, or acute myocardial dilation are also known to cause ST-segment shifts. Injury potential can be caused simply by applying pressure to the epicardial electrode. A cotton wick electrode soaked in saline is therefore preferable to solid electrodes

Analysis of ST-segment elevation for quantitative estimation of ischaemic injury is an empirical method. Recently serious criticism has arisen mainly because it was found that ST-segment elevation in the centre of a large infarct occasionally disappeared as the area of infarction increased The paradoxical reduction in ST-segment elevation in the centre of a large infarct has been theoretically explained based on the solid angle theorem (21) However the phenomenon is only observed in very large infarcts and is readily explained by intramyocardial conduction defects reflected in increased QRS duration. The epicardial ST-segment analysis therefore is applicable only when QRS is less than 0 06 seconds in dogs and less than 0 10 seconds in man. The time-point for reading of the ST segment elevation is crucial and should be standardized. Most authors have suggested 20 or 40 msec after end of the QRS complex. Whether the TP or PQ interval is the appropriate baseline is debatable One or the other should be used (21)

The importance of temporal ST-segment changes during prolonged coronary occlusion to prognosticate evolution of myocardial necrosis has not been clearly defined. A rapid transition of the myocardial damage into irreversible injury might start as early as 20—30 minutes after coronary occlusion, depending on the amount of residual flow Without intervention, epicardial ST-segment elevation decreases in the first few hours during uncomplicated myocardial infarction, but there is no intelligible relation between the decline in ST segment elevation and the evolution of necrosis. However ST-segment elevation reappears during interventions designed to increase infarct size conversely an abrupt reduction might be observed when coronary re-perfusion is started within 6 hours after occlusion (23 24). The ischaemic area might undergo necrosis and yet ST segment elevation can persist, as seen in large transmural infarction. The quantitative interpretation of ischaemic ST-segment elevation therefore becomes obscured when the myocardium undergoes necrosis Although directional changes in ST-segment elevation follow interventions in the experimental model

tion of precordial ST-segment elevation has appeared useful for determining infarct ex tension (35 36), its usefulness for detecting the influence of drugs on the ischaemic injury is debatable. *Pelides et al. (37) obser* ed a marked reduction in precordial multispot recording of ST-segment elevations when β-receptor blockade was induced as late as 72 hours after the onset of symptoms. Similar reductions were also obtained in patients with ST-segment elevation persisting as long as 9 days after the onset of infarction when there was no enzymatic evidence of necrosis (34) Because ischaemic ST-segment elevation signals more than 50 % reduction in myocardial flow relative to myocardial oxygen requirement, inevitably leading to rapid necrosis, t is dif ficult to reconcile tha persisting ST-segment elevation should reflect reversible ischaemic injury long after ecrosis has ended. The alidity of reduction of ST-segment height due to *intervention later than 6* hours after onset of symptoms should therefore be considered with care and more than 50 % reduction of ST-segment elevation should be required. W thin these limits re duction of ST-segment elevation has been observed with drugs such as hyaluronidase (38) nitroglycerine (39) and β-pyridylcar binol (40) and also with inhalation of 40 % xygen (41)

QRS-changes

Appearance of Q waves correlate well with entriculographic abnormalities (42), specifically the extent of dyssynergia, and inver sly with ejection fractions (43). Post-mor tem studies ha shown good correlation *between QR amplitude changes in conven*tional 12 leads ECG and the actual anatomical extent of anterior infarcts, but poorer correlation to posterior infarcts (44). Recently Hillis et al (9) suggested that precordial mapping of early ST-segment eleva tion and later development of QR changes should be combined to assess the effects of interventions on a myocardial infarct size. By determining how many sites with initial evidence of ischaemia (ST-segment elevation) progress to evidence of necrosis (QR amplitude changes) the effect of intervention can be evaluated in groups of patients

QR amplitude changes will only grossly reflect the conformational changes which take place in the whole spatial QRS complex due to necrosis. Furthermore, posterior infarcts and infarcts in the right ventricle are not readily reflected in precordial QR amplitude changes. More recently therefore we suggested the use of orthogonal vector loops for determining the evolution of an infarction (40). The mean spatial QRS vec tor is calculated sequentially during the evolution of necrosis, and by vectorial subtrac tion, a temporal infarct ector can be obtai ned. The evolution of the infarct vector in uncomplicated infarcts progresses exponentially parallel to but preceding the ac cumulated CK curve by 2—3 hours (Fig. 5)

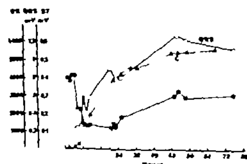


Fig. 5 Temporal changes in the QRS infarct vector accumulated CK and ST-segment vector in patient with acute myocardial infarction. The patial QRS and ST vectors were obtained from an orthogonal lead system (Frank) and the infarct vector was derived by ectorial subtraction f subsequent QRS vector recordings.

Interventions aimed at reducing infarct size have been shown to halt the evolution of the QRS infarct vector (Fig. 6). The use f QRS vector loop analysis has the advan tage that any change the QRS complex contributes to the spatial infarct vector Consequently the precision is increased and

mediately when a defined necrosis is abruptly caused by myocardial formalin injection and remain constant during subsequent hours (26)

QRS changes are closely related to the irreversible loss of tissue due to abolition of membrane action potential in subjacent myocardial tissue Local injury potential can no longer be elicited by applying pressure to the epicardial electrode (27) In ischaemic myocardium, the QR changes in epicardial leads evolve with time. The ultimate QRS complexes in epicardial sites are correlated with the subjacent extent of necrosis, measured histochemically and histologically (9) When the ratio between the increase in Q wave and reduction in R wave is used, an index is obtained which is closely related to the extent of subjacent myocardial necrosis and also to the 15 minutes ST-segment elevation in the same position (9) The amplitude changes of Q and R waves were used to evaluate interventions aimed at reducing infarct size in dogs. The height of early ST-segment elevation in epicardial sites was quantitatively related to later development of QRS amplitude changes. Consequently the effect of interventions can be studied with respect to the progression of QR changes relative to the initial ST-segment elevation.

Studies in human

ST-segment elevation

Precordial ST segment mapping has been applied in patients to delineate changes in myocardial ischaemia (8 28) Animal experiments have demonstrated that the extent and magnitude of ST segment elevations in 35 precordial leads correlated quantitatively with ST segment elevations in epicardial leads during coronary occlusion and varied appropriately with interventions (8, 29) The technique, however applies only to patients with anterior wall infarction, because of the relative insensitivity of diaphragmatic located infarcts in the conventional 12 lead electrocardiogram (8)

Precordial mapping of ST-segment height can only be used to assess directional changes in the ischaemic injury As many as 72 precordial electrodes have been used. The large number of leads offer little advantage in sensitivity compared with the use of selected electrode positions displaying the largest ST-segment elevation. Because recording and measurements of multiple electrocardiograms are timeconsuming and awkward to the patients, selected electrode positions have been preferred. Recently continuous recording of average ST elevation from 35 precordial leads were obtained by computer analysis (30)

Akiyama et al (31) suggested the use of an orthogonal lead system. Instead of averaging ST-segment elevation in multiple precordial electrodes, vectorcardiography permits the calculation of one spatial ST segment vector Good correlation was found between a precordial map of ST-segment elevation and the spatial ST-segment vector The study also suggested that inferior wall myocardial infarction can be evaluated by vector analysis. Epicardial electrocardiographic recordings of an infarct depends critically on the distance and orientation of the recording electrodes relative to the infarct, body build, skin resistance, and accompanying pericarditis. ST segment mapping is therefore limited to be used when the patient serves as his own control it is not valid for comparisons among different patients (8 32) A significant but weak correlation has been found between ST-segment elevation within the first hour after onset of symptoms and the ultimate infarct size evaluated by creatinephosphokinase (MB—CK) isoenzyme but no correlation was found when ST-segments were obtained more than one hour after the onset of symptoms (33).

The ST-segment elevation decreases slowly to normal values in uncomplicated myocardial infarction, but can remain elevated long after myocardial enzyme release has ended (34) ST-segment elevation remains high in patients with extensive transmural myocardial infarction and congestive heart failure and major increase in the ST segment strongly suggests a fatal outcome or reinfarction (35). Althorgh the determina

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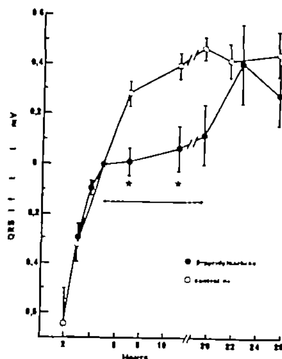


Fig 6 The effect of inhibition of lipolysis on the evolution of the spatial QRS infarct vector in patients (40) After more than one hour observation period the patients were randomized to either treatment with β-pyridyl-carbinol or no treatment (control).

its use is also extended to posterior and right ventricular infarcts. Sequential evaluation of QRS changes might have potential value in reflecting the extent and rate of necrosis development, but its practical use still awaits further trials.

Despite its shortcomings, the electrocardiographic technique offers an instant and simple way to monitor infarct evolution As yet, no other method is available that can effectively presage at the bedside the effect of the myocardial insult.

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LD-isoenzymes

The five common LD isoenzymes are named in order of rapidity of migration toward the anode in an electrophoretic field. LD_1 is the fastest and LD_6 the slowest in conventional systems. Each isoenzyme is a tetrameric unit composed of four subunits of two possible types. The physical properties of individual isoenzymes are determined by the relative percentage of each type of subunit contained (44). Extracts of myocardium contain primarily LD_1 and small amounts of LD_2, whereas those from liver or skeletal muscle contain mostly LD_4 and LD_5. Separation of LD is generally performed by chemical fractionation techniques, such as heat stability (LD_T), resistance to inhibition by urea (urea stabl LD), or affinity for alpha-hydroxybutiric acid as a substrate (αHBD). Several reports refer to the results of the different separation techniques (LD_1 LD_T urea stabl LD αHBD) as "heart" LD But none of these fractions of LD are specific of myocardial necrosis. Elevation of "heart" LD activity has been reported after renal infarction (3) and in about 25 per cent of patients with myocarditis (9). Furthermore, the rise of serum "heart" LD activity relatively late after AMI suggests that "heart LD elevations might reflect, in part, the release of enzymes from nonmyocardial components, such as red ells or inflammatory cells participating in the reaction to infarction within the heart (65).

However the primary disadvantage in using elevated "heart LD activity in the diagnosis of AMI is that red blood cells contain substantial amounts of "heart LD thus minimum haemolysis in blood sample will elevate the activity of this isoenzyme (4)

None the less, the long half lif of "heart LD is ad antageous in certain cases. In typical patient with AMI "heart" LD activity exceeds the normal range within abou 12 hours from the onset of symptoms, reaches peak in 48—60 hours, and declines to the normal range within 8—10 days (64). This prolonged rise is of advantage in patients with a long delay between onset of symptoms and admittance to hospital.

CK-isoenzymes

CK is a dimeric molecule composed of tw types of monomer the M (muscle) and the B (brain) subunits (12). Combinations of these subunits result in the occurrence of the three isoenzymes of CK designated CK MM, CK—BB, and the hybride CK—MB. Electrophoretic separation of CK was first performed by Burger and associates (8) and was followed by others (15 31 61). These isoenzymes are found in differing proportions in various tissues, the CK—MM isoenzyme in large quantities in skeletal muscle and CK—BB mainly in nervous tissue. The myocardium contains both CK—MM and CK—MB, but ther are divergent reports concerning the ratio between the two isoenzymes (13 33 35 56, 70 73). However many authors have considered CK—MB as cardiospecific (22, 47 59 73) this statement is further discussed later in this review Recently a mitochondrialspecific form of CK has been reported in the guinea pig heart (53).

Determination methods

A number of procedures ha been reported for the separation and quantitation of the three isoenzymes. In general, these techniques involve an initial separation with the use of either electrophoresis (33 59 66) or ion exchange chromatography (28, 46) followed by either fluorometric or spectrophotometric quantitation. More recently immunological techniques (30, 80) and methods with specific activation of the CK—MB (55) have been reported. Generally lower activities of CK—MB have been reported with chromatographic techniques than with electrophoretic techniques. This finding was erified by Ogunro and associates (54) who compared their agarose gel electrophoresis technique with an ion exchange procedure (46) and with the di thiothreitol activ tion method described by Rao and associates (55). They found CK—MB activity with the electrophoretic techni-

Enzymes in acute myocardial infarction Diagnosis with special reference to creatine kinase MB isoenzyme

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Elevated serum enzyme activity has become a cornerstone in the diagnosis of acute myocardial infarction (AMI) Diagnostic enzymology was first associated with the diagnosis of pancreatitis, 1908 (78) In 1954 Karmen, Wroblewski, La Due and their associates demonstrated that aspartataminotransferase (ASAT GOT) and lactic dehydrogenase (LD LDH) activity in serum increased after AMI (32) Creatine kinase (CK CPK) was first described by Lohmann (42) and introduced into clinical medicine by Ebashi and associates (18) Elevation of CK after AMI was first reported by Dreyfus and associates (17) several reports soon followed (20 34 68) Determinations of ASAT LD and CK have since been widely used in the diagnosis of AMI

The activity of other enzymes, such as aldolase, malic dehydrogenase, isomerase, and isocitric dehydorgenase (ICD) can also increase after AMI (75) but the clinical use is limited.

However the three routine enzyme tests ASAT LD and CK are not specific for the myocardium higher concentrations of each of these enzymes might be present in other tissues.

Although ASAT activity increases in about 90 per cent of patients after AMI (21) elevated activity can also result from pulmonary embolism (11) myocarditis (51), pericarditis (75), tachycardia (60) hepatic congestion (74), primary hepatic or biliary tract disease (6) skeletal muscle disorders (2) infections (14), oral contraceptive ingestion (40) after surgery (41) after cardiac catheterization (48) and after electroconversion (37) It is worthy of note that elevation of ASAT activity within the normal range has been reported also after intramuscular injections (38 81).

By the same token, elevated LD activity is a sensitive but non specific indicater of myocardial damage, detectable not only in about 90 per cent of patients with AMI (64) but also in those with congestive heart failure (6) pulmonary embolism (69), haemolysis and megaloblastic anaemia (72), hepatitis (79) neoplastic disease (72) myxedema (25) and skeletal muscle trauma (41)

Elevated CK activity is seen in virtually all patients sustaining AMI (21 57) it can be seen with several diseases such as muscular dystrophy (18) pericarditis and myocarditis (29), paroxysmal tachycardia (27), pulmonary embolism (36), cerebrovascular diseases (1), myxedema (24) diabetic coma (76) and hypothermia (43) Elevated CK activity has also been reported after prolonged activity (26), after treatment with intramuscular injections (45) after surgery (16) after cardiac catheterization (48) after electroconversion (37) and after radiotherapy (49)

However a higher specificity can be achieved by the use of LD and CK isoenzymes.

LD-isoenzymes

The five common LD isoenzymes are named in order of rapidity of migration toward the anode in an electrophoretic field. LD_1 is the fastest and LD_4 the slowest in conventional systems. Each isoenzyme is tetrameric unit composed of four subunits of two possible types. The physical properties of individual isoenzymes are determined by the relative percentage of each type of subunit contained (44). Extracts of myocardium contain primarily LD_1 and small amounts of LD_2, whereas those from liver or skeletal muscle contain mostly LD_4 and LD_5. Separation of LD is generally performed by chemical fractionation techniques, such as heat stability (LD_T), resistance to inhibition by urea (urea stable LD), or affinity for alpha hydroxybutyric acid as a substrate (αHBD). Several reports refer to the results of the different separation techniques (LD_1, LD_T, urea stable LD, αHBD) as "heart" LD. But none of these fractions of LD are specific of myocardial necrosis. Elevation of "heart" LD activity has been reported after renal infarction (5) and in about 25 per cent of patients with myocarditis (9). Furthermore, the rise of serum "heart" LD activity relatively late after AMI suggests that "heart" LD elevations might reflect, in part, the release of enzymes from nonmyocardial components, such as red cells or inflammatory cells participating in the reaction to infarction within the heart (65).

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que to be twice as high as the other two techniques. Thus, it seems reasonable to explain much of the discrepancy in the literature concerning CK—MB activity by methodological differences.

Moreover most of the described methods are technically complicated and time consuming and this limits their clinical use. However recently a promising immunological technique using anti M antibodies has been presented (80) but it still needs further clinical evaluation.

Table I

Human tissue CK—MB distribution according to three references.

	Ogunro et al, 1977		Roberts et al 1975		Jockers Wretou & Pfleiderer 1975	
Tissue	Total CK-(* activity	MB %	Total CK-(* activity	MB %	Total CK-(* activity	MB %
Skeletal muscle	10 000	0	10 000	0	10 000	0—3
Heart	2.000	30	2.000	15	2.000	4—27
Stomach	1 000	0	400	0	200	2—6
Uterus	500	0	—	—	60	2—20
Brain	200	0	500	0	700	0
Thyroid	50	0	—	—	200	6
Kidney	10	0	20	0	10	0
Liver	2	0	5	0	1	0
Lung	—	—	40	0	50	0—4
Spleen	—	—	5	0	5	0

*) Total CK tissue activity is expressed as relative total CK activity per gm tissue. The activity in skeletal muscle is set at 10 000 units per gm tissue

Tissue distribution of CK isoenzymes

Table I shows the human tissue CK isoenzyme distribution according to Jockers Wretou and Pfleiderer (30), Roberts and associates (56) and Ogunro and associates (54) The total CK activity is expressed as relative CK activity per gm of tissue, and the activity of skeletal muscle is set at 10.000 units per gm tissue As can be seen there is a substantial discrepancy concerning the total CK activity and the percentage of CK—MB in most tissues except heart between the three references. Roberts and associates (56) using an ion exchange technique and Ogunro and associates (54) using an electrophoretic technique, found CK—MB activity only in the heart muscle. In contrast, Jockers Wretou and Pfeiderer (30) using an immunological technique, found CK—MB activity also in skeletal muscle, stomach, uterus, thyroid, and lung But the total CK activity in these tissues, except in skeletal muscle, is low A small proportion of CK—MB activity in skeletal muscle with high total CK activity and a large muscle mass might therefore be a source of error in the evaluation of an elevated CK—MB activity (77) Furthermore CK—MB activity has also been found in skeletal muscle in earlier studies (13 22, 62, 73)

Clinical use of CK-MB

No CK—MB activity was found in sera from healthy persons, according to three studies (30, 54 57), but Mercer and Varat (47) found 0—2 per cent CK—MB activity in similar sera compared to 4.5—20 per cent after AMI These authors also found a

CK—MB activity of 0—1.6 per cent in sera from postoperative patients, patients with renal failure, pneumonia, chronic lung disease, psychosis, cirrhosis, and from alcoholics. The total CK activity here was in the same range as after AMI. Smith and associates (63) reported elevated CK—MB activity in single cases of paroxysmal atrial fibrillation, pericarditis, and unexplained chest pain. Elevated CK—MB activity was detected consistently after cardiac surgery (10). In muscular dystrophy an elevated CK—MB activity was also reported, but was interpreted as heart muscle involvement (22). In contrast, no elevation of CK—MB activity was reported in association with noncardiac surgery (23), congestive heart failure without AMI (57), cardiac catheterization (57), intramuscular injections (33), or skeletal muscle trauma (57). In association with electrical countershock, a modest elevation of CK—MB activity occurred in 6 per cent of the patients (19).

Van Der Veen and Willebrands (73) first reported an elevation of CK—MB activity in patients with AMI. Several reports have confirmed this finding (35, 56, 63, 70).

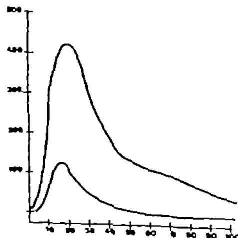


Fig. 1. A typical total-CK and CK—MB activity curve seen after an uncomplicated acute myocardial infarction. Hours on the abscissa and enzyme activity on the ordinate.

Figure 1 shows a typical CK—MB activity curve seen after an uncomplicated AMI. CK—MB activity exceeds the normal range within 4 hours after onset of symptoms, reaches a peak in an average of 15 hours, and declines to the normal range within 36 hours (4). The relative CK—MB activity at the peak has been reported to be 3—30 per cent of total CK activity (30, 57, 63). CK—MB reaches its peak value slightly earlier and declines more rapidly than total CK because of a somewhat higher fractional disappearance rate compared to those of CK—MM and total CK. This short duration of rise might limit the use of CK—MB, especially in patients with long delay between onset of symptoms and admittance to hospital. On the other hand, this could be an advantage, as an extension of an existing infarct might be discovered as a secondary rise in CK—MB activity. Furthermore, CK—MB could be of value in early diagnosis and early exclusion of an AMI.

A comparison of the different enzyme tests

There are several series that compare different enzymes in the diagnosis of AMI. All have the limitation of not absolutely defining AMI. Furthermore, a still unsolved problem is whether a small rise in enzyme activity can derive from reversibly injured myocardial cells (3, 71). A review of 25 series including 2,585 patients was presented by Goldberg and Winfield (21) who compared ASAT, αHBD and CK. Most of this series diagnosed AMI from the clinical picture and the electrocardiogram (ECG). In that review, 91 per cent of patients with AMI were found to have an elevated ASAT activity compared with 96 per cent for αHBD and CK. Table II presents three other series that compare both the sensitivity and the specificity of ECG and different enzyme tests (7, 58, 70). In these three series, the reference to each diagnostic parameter is the sum of the other diagnostic parameters in the same series. Table III sums up the series; it includes 719 patients.

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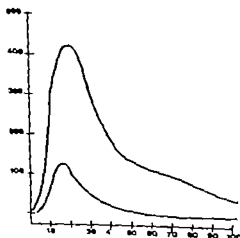


Fig. 1. A typical total-CK and CK—MB activity curve seen after an uncomplicated acute myocardial infarction. Hours on the abscissa and enzyme activity on the ordinate.

Figure 1 shows a typical CK—MB activity curve seen after an uncomplicated AMI. CK—MB activity exceeds the normal range within 4 hours after onset of symptoms, reaches a peak in an average of 15 hours, and declines to the normal range within 36 hours (4). The relative CK—MB activity at the peak has been reported to be 3—30 per cent of total CK activity (30, 57, 63). CK—MB reaches its peak value slightly earlier and declines more rapidly than total CK because of a somewhat higher fractional disappearance rate compared to those of CK—MM and total CK. This short duration of rise might limit the use of CK—MB, especially in patients with long delay between onset of symptoms and admittance to hospital. On the other hand, this could be an advantage, as extension of an existing infarct might be discovered as a secondary rise in CK—MB activity. Furthermore CK—MB could be of value in early diagnosis and early exclusion of an AMI.

A comparison of the different enzyme tests

There are several series that compare different enzymes in the diagnosis of AMI. All have the limitation of not absolutely defining AMI. Furthermore, a still unsolved problem is whether a small rise in enzyme activity can derive from reversibly injured myocardial cells (3, 71). A review of 25 series including 2,585 patients was presented by Goldberg and Winfield (21) who compared ASAT, αHBD and CK. Most of this series diagnosed AMI from the clinical picture and the electrocardiogram (ECG). In that review 91 per cent of patients with AMI were found to have an elevated ASAT activity compared with 96 per cent for αHBD and CK. Table II presents three other series that compare both the sensitivity and the specificity of ECG and different enzyme tests (7, 58, 70). In these three series, the reference to each diagnostic parameter is the sum of the other diagnostic parameters in the same series. Table III sums up the series. It includes 719 patients.

Table II

Comparison between different diagnostic parameters in three different series

Reference	Parameter	Sensitivity (%)	Specificity (%)
Wagner et al, 1973	ECG	66	100
	LD_T	90	95
	CK	98	85
	CK—MB	100	99
Blomberg et al 1975	ECG	64	100
	ASAT	100	90
	LD_T	98	91
	CK	100	89
	CK—MB	95	100
Roark et al 1976	ECG	78	100
	ASAT/LD	98	89
	CK	100	65
	CK—MB	96	100

According to Smith and associates (63) CK—MB is a more sensitive indicator of myocardial damage than enzyme tests hitherto available, but as Table III shows, the sensitivity of the different tests are fairly similar and outstanding compared with ECG An even more sensitive method for determination of CK—MB activity would probably be of value for detecting small amounts of myocardial damage. Furthermore, the sensitivity of an enzyme test as a diagnostic of AMI can also be increased by shortening the sampling intervals (50 67)

CK—MB isoenzyme has been said to be cardiospecific" (22, 47 59 73) and as

Table III

Comparison between different diagnostic parameters The sum of the three series presented in Table II (n = 719)

Parameter	Sensitivity %	Specificity %
ECG	69	100
ASAT	99	89
"heart" LD	95	92
CK	100	80
CK—MB	97	100

Table III shows the specificity of ECG and CK—MB is set at 100 per cent. This specificity is clearly superior to the other enzyme tests. However ASAT "heart" LD and CK might individually lack specificity but the combination of these enzyme tests with the addition of alaninaminotransferase (ALAT GPT) will probably give a specificity almost equal to CK—MB Moreover this combination of conventional enzyme tests can also give important information about complications of the AMI such as liver congestion.

At present, CK—MB is the single most specific test for AMI but it must not be regarded as truly specific for the myocardium As pointed out in this review elevation of CK—MB activity has been reported in conditions other than AMI or heart diseases. There is still a great discrepancy in the literature concerning the CK—MB activity in different tissues, and the practical implication of a potential CK—MB activity in skeletal muscle has already been discussed. However this single enzyme specificity makes the test unique in the diagnosis of AMI in association with non-cardiac surgery in states of shock, and in other clinical states, when the conventional enzyme tests are disturbed (63)

Conclusions

A review of the literature of CK—MB suggests that

1) CK—MB is a sensitive test in diagnosis of AMI, limited by its short duration of rise.
2) CK—MB is today the single most specific enzyme test for AMI most suited in diagnosis of AMI in various clinical situations when the conventional enzyme tests are disturbed
3) The early rise and short half life of CK—MB might be of value in early diagnosis and early exclusion of AMI Furthermore, these qualities might also be f value in studies of the evolution of AMI.
4) There is still considerable discrepancy in the literature concerning the CK—MB activity in different human tissues. This could be due, at least in part, to methodological differences. At present CK—MB should not be considered as 100 per cent heart specific.
5) A rapid and simple method for separation and quantitation f CK—MB is needed to permit more widespread use of this isoenzyme.
6) More clinical experience is needed for further evaluation f this test.

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Radionuclides in acute myocardial infarction

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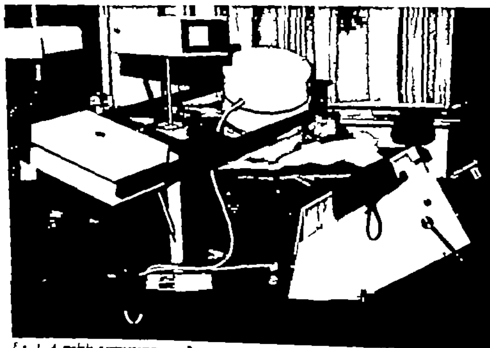


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Radionuclides in acute myocardial infarction

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The history of cardiovascular nuclear medicine is intimately related to the development of nuclear medicine and to the desire of cardiologists to find procedures less traumatic than catheterizations (4 39). These factors combined with difficulties of diagnosing ischaemic heart diseases in some patients, due to previous pathological ECG and equivocal enzyme response, led to the use of radionuclide methods in this group of patients. Most patients with suspected acute myocardial infarction are usually immobile during the first phase of their disease and are monitored in coronary care unit.



Fig. 1. A mobile gammacamera — Portacamera II (General Electric). Bedside examination shown.

Radionuclide methods were not available to the cardiologist, despite the development of better radiopharmaceuticals, until the recent development of the mobile gamma camera (fig 1) This brought bedside nuclear medicine into the coronary care unit (45)

The employment of radionuclide methods in the diagnosis and evaluation of patients with acute myocardial infarction followed mainly three directions (Table I)

Table I Methods used in cardiovascular nuclear medicine

1 Positive infarct scintigraphy — substances accumulating in necrotic myocardium
   ^{203}Hg Mercurascan
   ^{67}Ga
   ^{99m}Tc pyrophosphate
   ^{99m}Tc tetracycline
   ^{99m}Tc-glucoheptonate
2. Negative infarct scintigraphy — substances accumulating in normal myocardium
   ^{43}K
   ^{86}Rb
   ^{131}Cs
   ^{129}Cs
   ^{201}Tl
   $^{13}NH_4+$
   ^{54}Mn
   ^{11}C Palmitic acid
3 Radiocardiography hemodynamic assessments
   ^{99m}Tc human serum albumin
   ^{99m}Tc-erythrocytes

1) Positive" infarct scintigraphy with substances accumulating in infarcted myocardium. Among the first substances described were mercury isotopes, such as ^{203}Hg tagged to hydroxymercuryfluorescein (33) which gave satisfactory results in dogs with induced acute infarct (18, 25 42) these never succeeded clinically

Recently a different group of substances, mainly phosphates labelled with ^{99m}Tc, were shown to be clinically applicable in the diagnosis of acute myocardial infarction Bonte and coworkers (6) showed that a pyrophosphate labelleled with ^{99m}Tc accumulated in acutely infarcted myocardium. Later others verified this (16 28 35 56) ^{99m}Tc pyrophosphate proved extremely useful in diagnosing peri- and postoperative myocardial infarctions (32, 41) in this clinical setting enzymes and ECG cannot be used after cardiac surgery

^{99m}Tc, obtained as a daughter product of ^{99}Mo, has a half life of 6 hours and gamma ray energy of 147 keV Thus it is suitable for the low energy mobile gamma cameras

The mechanism behind the pyrophosphate uptake is obscure but it has been postulated that pyrophosphate has an affinity to hydroxyapatite crystals formed in the mitochondria when the myocardial cells undergo necrosis (8 49 50) Several groups (12, 20 48) recently presented evidence that pyrophosphate is taken up mainly by irreversibly damaged myocardial cells. These might still have some perfusion left (55) thus enabling pyrophosphate to reach them.

Simultaneously with the development of ^{99m}Tc pyrophosphate, other agents, such as ^{99m}Tc tetracycline (23 24) and later ^{99m}Tc-glucoheptonate (26), were introduced as infarct labelling agents. However both these substances have largely been abandoned, as the interval between injection of the radionuclide and the imaging procedure was too long, allowing other parameters to provide the diagnosis.

2) "Negative" infarct scintigraphy using substances accumulating in normal myocardium. These radionuclides are believed to reflect regional myocardial perfusion, and when the perfusion is decreased, a perfusion defect appears in the scintigram. The substances in this group are potassium-43 (57) and its analogues. Several have been used, such as ^{86}Rb (11) ^{131}Cs (4 12) and ^{129}Cs (44) All of them had a gamma energy level more suitable for the rectilinear scanner than for the gamma camera thus their clini

cal applicability was limited. Recently another potassium analogue, [201] Tl, was introduced (27) and proved to be a very useful tool in the diagnosis of acute myocardial infarction (19 52, 54). It has two energy levels, (80 and 167 keV), both being ideal for the low energy mobile gamma cameras. The long half life (about 72 hours) eliminates the disadvantage of being a cyclotron produced product.

The potassium analogues reflect the function of the sodium-potassium pump within the myocardial cells. When the myocardium is perfused, a significant amount of potassium is withheld intracellularly. If the perfusion is decreased, the amount of available potassium is also decreased thus a perfusion defect in the scintigram will appear. From this, it is apparent that no differentiation of the age of the perfusion defect is possible with these radionuclides.

Masero and coworkers (34) showed that potassium or its analogues are largely extracted by the myocardium during the first circulatory pass, and when evenly mixed with the blood, are distributed proportionally to the cardiac output (46).

3) Radiocardiography where the left ventricular function and wall motion are studied. Ventricular function can be measured non-invasively by two methods. First by recording the initial passage of a bolus injected blood pool tracer through the heart, first pass study which Ashburn and Schelbert utilized (47). The first pass method utilizes a recording of the time-activity curve over the left ventricle that has peaks and valleys corresponding to end-diastole and end-systole (Fig. 2)

Second by data recording after the tracer has equilibrated. An ECG-gate and the scintillation camera is used so that images

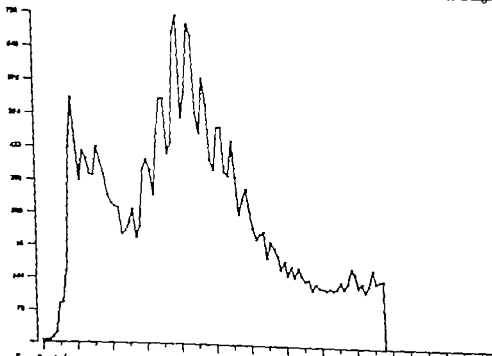


Fig. 2. A first passage curve exemplified. The ejection fraction in this patient was calculated to be 41 %.

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These techniques make possible early diagnosis of acute myocardial infarction (29). Willerson and coworkers found positi e pyrophosphate scintigrams already 12 hours after the onset of symptoms. Wackers et al found that perfusion defects with ^{201}Tl could be diagnosed as early as 6 hours after the onset of symptoms. In W ckers series all patients examined before 6 hours after the onset had developed perfusion defects in areas later corresponding to ECG-localization of the infarct (54).

Clinical study

All these methods were used in patients admitted to the coronary care unit of the Malmö General hospital with primary clinical suspicion of acute myocardial infarction due to sever chest pain, pulmonary oedema, dysrythmias, and dyspnea.

The clinical diagnosis of acute myocardial infarction was based on any of the following criteria

1) Subjective symptoms in combination with typical QRST-changes in the ECG
2) Subjective symptoms in combination with two elevated enzyme alues (S-ASAT S-LD)
3) Typical QRST-changes in the ECG in combination with two elevated enzyme alues
4) Autopsy data (21 28)

I contrast, the diagnosis of unstable angina pectoris was based on a combination of the following criteria

1) Previous stable angina, or angina of recent onset with progressiv increase in severity of symptoms
2) Angina rest with recurrent episodes lasting more than 20 minutes and poorly relieved by nitrates
3) No elev tion of serum enzymes
4) Transien ST T changes that frequently return to normal after the ttack (10, 4)

All 350 patients were examined with 10 mCi ^{99m}T -pyrophosphat (Byk Mallincrodt, USA, Solcoscint, Kabi Diagnostica, Diagnostics inc., USA) 125 patients were also investigated with 1.5 mCi ^{201}Tl (Phil ps Duphar the Netherlands) In 48 patients, different hemodynamic evaluations were also made. A mobile gamma camera, Portacamera II B or C (General Electric, USA) was used with a standard low-energy parallel hole collimator The scintigrams were obtained in anterior — posterior left 30 anterior oblique and left lateral positions. All were evaluated for presence, absence, size, localization, and intensity of an uptake or defect. When radiocardiography was performed, the left ventricular ejection frac t on was counted if a gated study was undertaken, the wall motion was estimated.

Results

Of the 350 pyrophosphate examinations, 64 showed positive uptakes (Table II) In the group of 188 patients with acute transmural infarction, 180 showed radionuclide accumulation and well localized intense uptakes in 90 per cent. (Fig. 4) The correl



Fig 4 Myocardial scintigram with ^{99m}T -pyrophosphate recorded 90 minutes fter injection, in LAO 30° position A anterior grade 3 intense ptake was recorded in the patient with transmural anterior infarct. The recording was made with the Portacamer II c.



Fig 3 After injection of 15 mCi ⁹⁹ᵐTc-human serum albumin gated study was performed in this patient The upper panel illustrates end systole and the bottom panel illustrates end diastole No akinetic area can be recognized

are recorded during end systole and end diastole (40 43) (Fig 3) Gated studies have the advantage of being able to use several views after a single tracer injection, and are therefore more like regular angiography Both methods can be used to calculate the left ventricular ejection fraction, according to the following formula

LVEF = EDV — ESV/EDV — BKG

where

LVFF = left ventricular ejection fraction

EDV = end-diastole volume

ESV = end systolic volume

BKG = background

Several studies, independent (17) of each other have shown (17 51) correlation coefficients of 0 9 or better for ejection fractions obtained with radionuclide methods and angiography (37)

Impaired left ventricular function can then be diagnosed Left ventricular wall motion is best studied with gated blood pool studies, where diagnosis of akinetic and dyskinetic areas can easily be made.

Both methods have the advantage of accumulating data over a relatively short time. This allows them to be used rather easily in the coronary care unit. They can very easily be repeated several times during the patient's stay in the ward, and thereby yield information of his day to day hemodynamic situation It seems as though both methods, properly utilized, can predict left ventricular failure early (15 51) and also estimate the effect of treatment.

The indications for using radionuclide methods in cardiology are several and have been demonstrated by several reports. The following seem to be the major indications

a) Differentiation of origin of chest pain (47)
b) Previous pathological ECG e.g., bundle branch block, remaining ST T changes after previous infarcts in combination with chest pain postoperatively
c) Differentiation between new and old infarcts (54)
d) No adequate enzyme response, e.g alcoholism, liver pathology postoperatively
e) Hemodynamic assessment of the working capacity of the right and left ventricles during several phases of the infarct

Besides these, several reports by Botvinick and coworkers have shown that sizing of infarcted myocardium can be performed with ^{99m}Tc pyrophosphate (7) Holman and coworkers recently confirmed these findings (22) These results suggest that in the future it will be possible to judge the efficiency of decreasing the size of a necrotic area by pharmacological or surgical interventions

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tion between the uptake localization and ECG localization of the infarct was excel lent. All 5 patients with left bundle branch block but who fulfilled the criteria for acute myocardial infarction also exhibited well localized and intense pyrophosphate uptakes. The earliest uptake was registered in 10 patients examined 4 hours after the onset of symptoms.

Of the patients diagnosed as unstable angina pectoris, 73 per cent showed an uptake but this was distinctly different from the uptake in transmural infarcts, which also Ab ulla and coworkers found (1) These patients had low graded, diffusely spread uptakes (Fig 5)

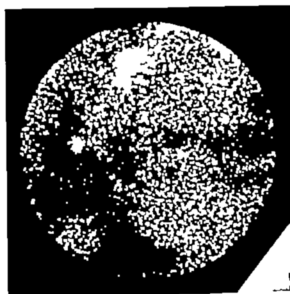


Fig 5 A 62 year old male with a diffuse low intense pyrophosphate uptake seen in combination with unstable angina pectoris

Positive uptakes were found in five patients with other cardiac diseases. One had Chagas disease (30) (Fig 6) and one, Prinz metal variant angina Two were found in patients with old infarcts and ventricular aneurysms, whi h also Ahmad (2) observed The final positive pyrophosphate scintigrams were registered in a patient who developed an acute myocardial infarction after defibrillation (Fig 7) a finding previously reported by diCola and coworkers (14)

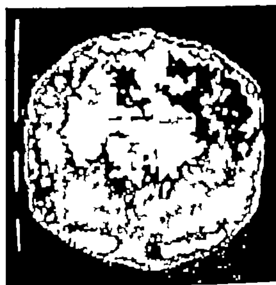
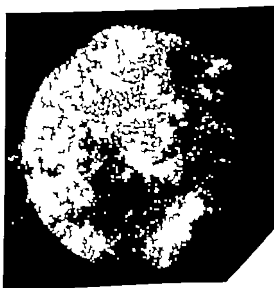


Fig 6 A b ge antero-lateral uptake with the intensity graded 3 The patient suffered from Chagas disease The scintigram mimicked the p ttern of transmural myocardial infarction.



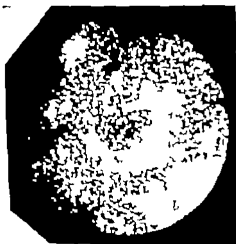
F g 7 A pyrophosphate uptake reco ded a patient fter transtho aci counter rrent chock

125 patients were also examined with ^{201}Tl. A very good correlation existed between a thallium defect and a pyrophosphate uptake (Fig 8) However seven Tl scintigrams showed perfusion defects where no new infarct could be verified in patients who had previously sustained infarcts.



Fig 8 An LAO 45° recording with ²⁰¹Tl in patient with an inferior transmural infarct. In the apical re Large perfusion d fect is seen The recording was made with Portacamera II 20 minutes f er injection.

In s of them the pyrophosphate examination remained negative and one t was questionably positive, probably owing to ventricular aneurysm. Five patients with unstable angina pectoris had perfusion defects (Fig. 9) thus making it impossible to



F g 9 The LAO 45° recording w th ²⁰¹Tl, in patient th unstable angina. Note the decreased perfusion in be antero-septal region

separate them from those with acute myocardial infarction. A similar finding was recently reported by Wackers and coworkers (53). No false negative has been reported with ^{201}Tl-scintigraphy

Gated thallium studies have also been performed with a pin hol collimator (focusing on the septum) which has been utilized when septal nfarcts or conduction disorders were present (Fig. 10)

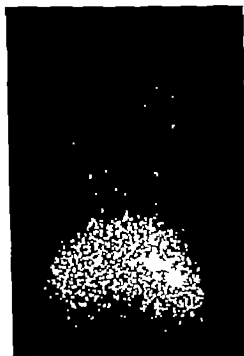


Fig 10 A gated ²⁰¹Tl-study performed with pin hole ollimator in patient with left bundl branch block. The pper panel illustr tes end-systole and the lower end-diastole I the lower panel perf sion defect is seen in the septal region.

Conclusions

It can be concluded that both ^{99m}T -pyrophosphate and ^{201}Tl are useful aids in the diagnosis of acute myocardial infarction, as Parkey and several others have shown (29 38 5) Both methods ha a high degree of

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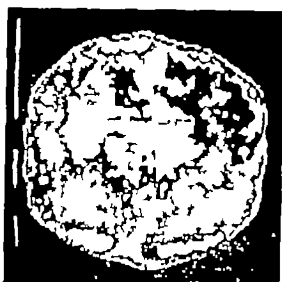


Fig 6 A huge antero-lateral uptake w th the intensity graded 3 The patient s ffered from Chagas disease The scintigram mimicked the pattern of transmural myocardial infarction.



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sensitivity and specificity and rarely show false negative results. False positives appear in patients with unstable angina pectoris or with old infarcts, and this applies for both radionuclides. The decision about which radionuclide method or combination is most useful in the evaluation of a specific patient with chest pain largely depends on the clinical situation and the questions being asked. If an acute diagnosis is looked for ^{99m}Tc pyrophosphate seems to be the isotope of choice, judging by the evidence in the literature (53 56) In a patient where all clinical evidence supports the diagnosis of myocardial infarction but where any of the laboratory parameters fail ^{201}Tl seems to be the ideal isotope for the subacute situations. Several authors (54) recommend ^{201}Tl when it is a question of silent and old infarction

Any combination with radiocardiography seems to be feasible when the left ventricular function should be studied in a patient with or without an established acute myocardial infarction.

If any method, either positive or negative infarct scintigraphy yields a positive result, the probability that the patient has an acute infarction is more than 85 per cent. This at least equals the sensitivity of the otherwise routinely used clinical methods (20 22). The possibility of differentiating between unstable angina pectoris and myocardial infarction (29 56) adds another important dimension to these methods. Combined with radiocardiography and determination of left ventricular function it adds a new important, and powerful tool in the evaluation of patients with acute myocardial infarction.

Table II Summary of the result with ^{99m}Tc-pyrophosphate

Number of patients	*Diagnosis*	*Positive pyrophosphate scintigrams*	*Negative pyrophosphate scintigrams*
188	Transmural AMI	180	8
5	Left Bundle Branch block with AMI	5	0
22	Subendocardial AMI	22	10
75	Unstable angina pectoris	52	23
29	Other cardiac disorders	5 (*1 Chagas, 1 Prinzmetal,* 2 ventricular aneurysms, 1 post defibrillation)	24
21	Non-cardiac disorders	0	21

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sensitivity and specificity and rarely show false negative results. False positives appear in patients with unstable angina pectoris or with old infarcts, and this applies for both radionuclides. The decision about which radionuclide method or combination is most useful in the evaluation of a specific patient with chest pain largely depends on the clinical situation and the questions being asked. If an acute diagnosis is looked for ^{99m}Tc pyrophosphate seems to be the isotope of choice, judging by the evidence in the literature (53 56) In a patient where all clinical evidence supports the diagnosis of myocardial infarction but where any of the laboratory parameters fail ^{201}Tl seems to be the ideal isotope for the subacute situations Several authors (54) recommend ^{201}Tl when it is a question of silent and old infarction.

Any combination with radiocardiography seems to be feasible when the left ventricular function should be studied in a patient with or without an established acute myocardial infarction.

If any method, either positive or negative infarct scintigraphy yields a positive result, the probability that the patient has an acute infarction is more than 85 per cent. This at least equals the sensitivity of the otherwise routinely used clinical methods (20, 22) The possibility of differentiating between unstable angina pectoris and myocardial infarction (29 56) adds another important dimension to these methods. Combined with radiocardiography and determination of left ventricular function it adds a new important, and powerful tool in the evaluation of patients with acute myocardial infarction.

Table II Summary of the result with ^{99m}Tc-pyrophosphate

Number of patients	*Diagnosis*	*Positive pyrophosphate scintigrams*	*Negative pyrophosphate scintigrams*
188	Transmural AMI	180	8
5	Left Bundle Branch block with AMI	5	0
22	Subendocardial AMI	22	10
75	Unstable angina pectoris	52	23
29	Other cardiac disorders	5 (1 Chagas, 1 Prinzmetal 2 ventricular aneurysms, 1 post defibrillation)	24
21	Non-cardiac disorders	0	21

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Renal tubular resorption and storage of myoglobin have been documented (3, 2). With increasing plasma levels, tubular resorption of myoglobin also increases. Probably only when this absorptive capacity (Tm) is exceeded will myoglobin appear in urine. Thus, free myoglobin might be handled by the nephron in manner similar to glucose, phosphate, uric acid, hemoglobin, amino acids, and other proteins (4). The catabolism of myoglobin in the body is similar to that of hemoglobin. Bywaters (6) observed hyperbilirubinemia in man in clinical states of muscle damage and myoglobinuria. The fate of the globin portion is not known. Probably cathepsinlike proteolytic factors are involved. Kagen and Gurevich (12) found these properties in tissue extracts, cardiac muscle, liver, spleen, and urine. Under acid conditions in the presence of these extracts, myoglobin lost its antigenic properties. Moreover the kidney might be important in the breakdown of proteins small enough to be filtered (5).

Laboratory aids in diagnosing myoglobinemia and myoglobinuria

The diagnosis of myoglobinuria and/or myoglobinemia has in the past been regarded as difficult. The first step toward identification of myoglobin in a sample of urine is usually to test for "occult blood" with an assay that relies upon the enzymatic property of myoglobin to release oxygen from hydrogen peroxide. A dye such as toluidine, which develops color in the presence of oxygen, makes this reaction easily perceptible. This test is sensitive and can detect 5 to 10 µg per ml, and in certain urines, even smaller amounts. By using a test paper technique for estimating small amounts of urinary glucose (28) Urang *et al* (31, 32) succeeded making the peroxidase test still more sensitive — less than 1 µg/ml. However all tests based on the peroxidase activity of myoglobin lack specificity for myoglobin; they will react also for hemoglobin.

Electrophoresis on a variety of supporting media (paper, starch, cellulose acetate, acrylamide gel), precipitation methods with ammonium sulfate, spectrophotometry, and isoelectric focusing are techniques difficult to interpret in the presence of denaturated protein.

Immunological methods have been the most sensitive and precise. Specific antisera, which do not react detectably with hemoglobin or other constituents of serum, urine, or muscle tissue, allow detection of myoglobin at a level of sensitivity greater than with other techniques. Precipitin methods permit detection of 5 to 10 µg per ml; complement fixation and hemagglutination methods increase the sensitivity to 1 µg/ml. The use of ^{131}J myoglobin and anti-human myoglobin in a radioimmunoassay allows 0.5 ng of myoglobin to be determined. However, even if highly sensitive methods are used for the detection of myoglobin in serum or urine, care must be exercised in the interpretation in view of the above-mentioned chemical, physiological, and metabolic factors affecting myoglobin.

Myoglobinuria and myoglobinemia in myocardial infarction

Myoglobinuria is generally considered uncommon, although it has been reported in a wide variety of clinical conditions (26). In 1956, Kiss and Reinhart (15) were the first to find myoglobin in serum and urine of patients after myocardial infarction. Highest levels were noted in the first days of illness. They used complicated precipitation technique with ammonium.

Despite immunological methods for the determination of myoglobin having been available since 1928, it is only during the last 10 years that they have been developed for differentiating myoglobin from hemoglobin. In 1966, Stramer *et al* (30), using antibody precipitin techniques, detected myoglobin in the urine of patients after myocardial infarction. Due to the lack of specificity the test was forgotten, and the question of myoglobinuria as an aid in the diagnosis of myocardial infarction remained open until 1970, when Adams and Elliot (1) reported myoglobinuria after cardiac infarction. They used a qualitative hemagglutin-

Myoglobin

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In 1897 Mörner (21) prepared the muscle pigment from dogs. In a classical study he demonstrated spectrophotometric differences between the pigment and hemoglobin and suggested a new name for it myoglobin

In clinical medicine, it is important to know whether or not myoglobin is released into the circulation as a result of infarction of heart muscle. The recognition of myoglobinemia and/or myoglobinuria might be of diagnostic and prognostic importance, as the amount of myoglobin released should indicate the extent and severity of muscle damage (13). Substantial evidence suggests that damage to the cardiac muscle mass causes the release of various intracellular enzymes into the circulation. The importance of determination of serum enzyme activity profiles of ASAT ALAT LD-isoenzymes is well documented. A promising approach is the quantification of creatine phosphokinase (CK) by measurement either of total enzyme activity (25) or of the activity of its cardiac-specific fraction CK—MB. A similar high degree of specificity has been attributed to arginase (23) and glycogen phosphorylase (16) in the early differential diagnosis of myocardial infarction. Determination of serum adenylate kinase activity (8) seems to offer interesting prospects in the early diagnosis of myocardial infarction.

It seems worth while to encourage all studies directed toward new diagnostic procedures that can help us to improve our diagnostic acumen in acute myocardial infarction and ultimately to indicate the extent of the injury. Prognostic indices should in future include some measurement of infarct size (17).

Some chemical physiological, and metabolic aspects of myoglobin

Kagen and Gurevich (11) showed that myoglobin was localized to three regions in the muscle cell transverse striations of the contractile elements, sarcolemmal regions, and intracellular membranes of fibrillar structures. Myoglobin has a molecular weight of approximately 17 000 daltons.

When released from muscle at injury or disease, myoglobin can enter the circulation and from there be cleared by renal mechanisms. Haptoglobin does not bind human myoglobin (9). Lathem (18) studying canine myoglobin, found significant binding of this protein by canine plasma. The maximum binding averaged 21 mg per 100 ml of plasma. At concentrations of myoglobin in plasma below this value, approximately 15 to 50 per cent of the myoglobin in plasma was in the unbound state. The myoglobin-binding protein appeared to be either an α_2 or a β-globulin.

In man the effective renal threshold is not known, nor is it known how important a role the plasma capacity plays in binding myoglobin in the prevention of renal excretion.

Renal tubular resorption and storage of myoglobin have been documented (3 2). With increasing plasma levels, tubular resorption of myoglobin also increases. Probably only when this absorptive capacity (Tm) is exceeded will myoglobin appear in urine. Thus, free myoglobin might be handled by the nephron in a manner similar to glucose, phosphate, uric acid, hemoglobin, amino acids, and other proteins (4). The catabolism of myoglobin in the body is similar to that of hemoglobin. Bywaters (6) observed hy perbilirubinemia in man in clinical states of muscle damage and myoglobinuria. The fate of the globin portion is not known. Probably cathepsinlike proteolytic factors are in olved. Kagen and Gurevich (12) found these properties in tissue extracts, car diac muscle, liver spleen, and urine. Under acid conditions in the presence of these extracts, myoglobin lost its antigenic properties Moreover the kidney might be important in the breakdown of proteins small enough to be filtered (5).

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nation inhibition test. Myoglobinuria was detected in 35 of 44 patients after myocardial infarction. However the specificity of this test was considered low as the tests were positive five times when no diagnosis of myocardial infarction was made.

Levine *et al* (19) used the same technique with an estimated sensitivity between 0 6 and 2 0 μg of myoglobin per ml of urine. Myoglobinuria was detected at least once during the illness in 92 per cent of the patients. On day one, the myoglobin test was positive in 89 per cent, on day two, in 87 per cent, and on day three, in 76 per cent.

The radial immunodiffusion assay described by Saranchack and Bernstein (27) is an example of differences in the sensitivity for myoglobin in urine of the immunological techniques. They found significant levels of myoglobin at or above 50 μg/ml in urine samples from 59 of 60 patients with myocardial infarction. Volk *et al* (33) studied myoglobin in serum by an immunological method using the technique according to Ouchterlony with a sensitivity of 15 μg/ml Myoglobin was released into serum in the first 30 minutes after the attack of pain. There was a distinct difference in titre between survivors and those who died They interpreted the influx of myoglobin to be a sequela to cardiogenic shock and hypoxemia. Therefore myoglobin is not found in sudden death

Since 1973 several reports have been published (20 22, 10, 24 34) where serum myoglobin levels have been measured by means of radioimmunoassay capable of detecting nanograms of myoglobin per ml of serum. With these methods, myoglobin has been identified in sera from normal adults it ranged from 6 to 85 ng/ml Raised myoglobin levels were present in all except two of 99 cases reported in total Stone *et al* (29) found a mean serum concentration of 528 ± 76 ng/ml They further report that only two of another 44 patients admitted with chest pain but without subsequent electrocardiographic, enzymatic, or technetium — 99m stannous pyrophosphate myocardial scintigraphic evidence of acute myocardial infarction had raised myoglobin levels the mean value for this group was within the normal range (44 ± 6 ng/ml).

Willerson *et al* (34) studied the relation between the histological infarct size in dogs and peak myoglobin serum levels and found a highly significant correlation ($r = 0.83$, $p < 0.01$) The serum myoglobin levels began to rise within two hours and peaked in six hours after experimentally induced acute myocardial infarction.

Kagen *et al* (14) and Donald *et al*. (7) found that urinary myoglobin levels, when measured simultaneously with serum, did not correlate well with the marked temporal changes that occurred in the serum. The variable myoglobin excretion pattern suggests that, in seemingly uncomplicated myocardial infarction, there is considerable variation between patients in the pattern of evolution of the infarction process.

Concluding remarks

The conclusion is that transient myoglobinemia seems to be one of the earliest laboratory abnormalities occurring in myocardial infarction therefore it should prove useful as a diagnostic aid in patients. Further studies are necessary regarding the prognostic value of myoglobinemia. Both chemical and immunological methods for demonstrating myoglobinuria require better documentation of their sensitivity before the value of detecting myoglobin in urine as a tool for diagnosing myocardial infarction can be determined.

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Morphological diagnosis of early acute myocardial infarction

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In recent years, much work has been done to find reliable morphological methods for diagnosing early myocardial infarction (1). The lack of them makes it impossible to compare the reliability of different clinical methods and creates difficulties in finding the mechanisms of death due to acute heart failure. Think of the discussions on the relation of coronary thrombosis to myocardial infarction! Patients dying shortly after a suspected infarction often show no coronary thrombus, but such cases could well be due to heart failure of noninfarction type and thus would not show any thrombus.

Many methods are available for use by morphologists (Table I). They can be divided into macro- and microscopical. There are also methods that use chemical analysis and the recently introduced methods that employ radioactive isotopes. However not only the myocardium should be studied also lesions of the coronary arteries are of prime importance. We look for fresh thrombi or other type of coronary occlusion. For instance hemorrhage in an atherosclerotic plaque or embolus, or perhaps only atherosclerosis with varying degree of stenosis. For judging coronary stenosis, post-mortem angiography is of value, especially in subjects with extensive calcifications. The disadvantage of such angiography is that it makes it more difficult or impossible to use other diagnostic methods, for instance chemical analysis or enzyme histochemistry.

The macroscopical changes of early infarction are pallor and softening corresponding to oedema. Most text-books state that myocardial infarction is detectable first after 12—18 hours, and this seems to be correct, although some pathologists claim to be able to diagnose an infarction macroscopically already after 4—6 hours. The macroscopical diagnosis can be improved by for instance, enzyme- and fluorescense stainings. The most used enzymatic method is based on the loss of dehydrogenase activity in ischaemic myocardium. This is shown by treating the myocardium with tetrazolium derivates, usually so-called nitro-BT (2). With this method, which is resistant against autolysis, myocardial infarcts can be diagnosed within 6—8 hours.

A further macroscopical method is fluorescence studies of the myocardium after intravenous administration of tetracycline compounds (3). In early stages, the infarcted area does not show any fluorescence after 1—2 hours, the fluorescence is concentrated to the zone between normal and ischaemic myocardium. This zonal fluorescence is stable in contrast to the one in the normal myocardium. In later stages, the tetracycline derivates are concentrated in the necrotic myocardium, which is then clearly demarcated. This method has mainly been used experimentally but it seems to be worth another clinical trial.

Regarding light microscopic diagnosis on

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I recent years, the use of radioactive isotopes for detecting myocardial ischaemia, both clinically and morphologically ha become popular (16, 17). Mainly tw me thods can be used either positive in which isotopes are concentrated in the necro tic myocardium, or negati where iso topes re concentrated in the normal myo cardium but not in the infarction. Examples f the latter type of isotopes are potassium and its analogues rubidium, cesium, and thallium. Of isotopes oncentrating in the infarcted myocardium, the prototypes are tetracyclines and principally technetium-labelled stannum-pyrophosphate. Both ty pes of isotope-diagnostic methods are used to show myocardial infarction clinically Morphological studies have shown that these methods are reliable for both quanti tative and topographic assessments.

What methods re then of practical use for diagnosis of early myocardial infarc tion? Ordinary light microscopy cannot po sitively diagnose an infarction that is younger than about 8 hours. By using tetra zolium technique, this period can be shorte ned by about 2 hours. A very reliable but more elaborate method is to study the potas sium- sodium rati in the myocardium, the time then being reduced to 1—2 hours. Dur ing the first three hours, different enzyme histochemical methods can be employed but autolysis might affect them. Fluorescent methods are of use within the first hours, but for the diagnosis of a recent infarction, tetracycline derivates should probably be used. If isotopes are given as soon as pos sible, study of their distribution within the myocardium will be of great value. These methods cannot be applied to all in stances of sudden heart death which occur outside the hospital. They are also difficult to apply to deaths within the hospital unless special arrangements are made to perform a post mortem soon after death. I such cases, there does not seem to be any better method than chemical determination during the first three hours after a suspected myocar dial infarction. During the next three hours, fluorescent and some enzyme histochemical methods can also be used.

Morphological diagnosis of early myocardial infarction

Coronary arteries

Macroscopial methods
Without aid
With aid

routine (hematoxylin-eosin) stained slides, the criteria laid down by Mallory and coworkers (4) and Lodge-Patch (5) are still used. The earliest change is oedema, which is noticable after about 2 hours. Four hours after the infarction the cell nuclei begins to become pyknotic and after about 6 hours, changes of the cytoplasm begin to appear i.e. increased eosinophilia, shrinking, and loss of cross striation. Infiltration of polymorph-nuclear leukocytes begins about now and this change seems to be one of the best signs of an infarction, as the other changes are identical with those appearing during autolysis. The leukocyte infiltration reaches its maximum after about 24 hours and persists for another one or two days and then slowly disappears. At the end of the first week, pigment filled macrophages appear together with lymphocytes and plasma-cells and fibro-blast proliferation. Later eosinophilic leukocytes might appear and collagen material is laid down. Proliferation of thin walled blood vessels begins at the end of the first week and reaches its maximum after about 4 weeks. All these changes are most pronounced in the edges of the infarction. In dating the age of an infarct, it is important to take the size of the necrosis into account.

A further histological method was published in 1972 by Bouchardy and Majno (6). According to them, it is always possible to find especially at the edge of an infarction, myocardial fibres that are stretched thin, and wavy. This change is said to appear very quickly certainly within an hour and possibly as early as two minutes after the infarction. But most pathologists seem very sceptical about this observation and other studies have not supported the method. None the less, several papers state that no such changes were found in recent myocardial infarction.

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Poley and coworkers (1) introduced a further special method in 1964 based on the observation by Selye (8) that myocardial fibres experimentally damaged by various toxins, showed eosinophilia when stained with acid fuchsin. Poley noted that this method was somewhat unreliable, but it was re-introduced by Lie (9) with the statement that this fuchsinophilia was a very good indication of myocardial ischaemia. This is certainly not our experience or that of others (10). Lie and coworkers (11) 1971 introduced the so-called HBFP (hematoxylin basic fuchsin-picric acid) staining which was said to be much more reliable and to be able to diagnose infarctions only a few hours old. Positive staining reactions were even reported already after 30 minutes. This positive staining, the so called fuchsinorrhagia, has been much criticised as most unreliable. Although papers exist in favour of this method (12) most authors deny its value (10, 13).

Fluorescense methods can also be used histologically. The previously mentioned tetracycline method (3) gives fluorescence on both fresh sections and formalin-fixed/paraffin embedded slides. Other methods that seem promising but which have been used experimentally are acridine-orange and astraphosphine staining the latter for showing accumulation of fat (14). Acridine-orange staining, which can be used on both fresh and formalin fixed material, shows ischaemic damage after about 3 hours on fresh myocardium and after about 5 hours on fixed material.

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Morphological diagnosis of early myocardial infarction

Coronary arteries

Macroscopical methods
- Without aid
- With aid

Tetrazolium derivates, nitro-BT
Fluorescence
Light microscopical methods
Routine-stained (Htx-eosin) slides
Traditional histologic criteria
Wavy myocardial fibres
Special-stained slides
PAS (periodic acid Shiff)
PTAH (phospho-tungstic acid hema tyxylin)
Acid fuchsin, fuchsinophilia
HBFP (hematoxylin basic fuchsin picric acid) fuchsinorrhagia
Fluorescence
Tetracyclin
Acridin-orange
Astraphosphin
Enzyme histochemistry
Dehydrogenases (succinyl lactate-malate- butyrat)
Phosphorylases
Phosphokinases
Electron microscopical methods
Morphology
Enzyme histochemistry
Chemical methods
Sodium (+) Potassium (—)
Calcium (+) Magnesium (—)
Isotope methods
Positive diagnosis
Technetium (stannium-pyrophos phate)
Tetracyclin
Negative diagnosis
Potassium, Cesium, Thallium

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Creatine kinase MB isoenzyme in diagnosis of acute myocardial infarction

Peer Grande, Claus Christiansen and Asger Pedersen

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Abstract

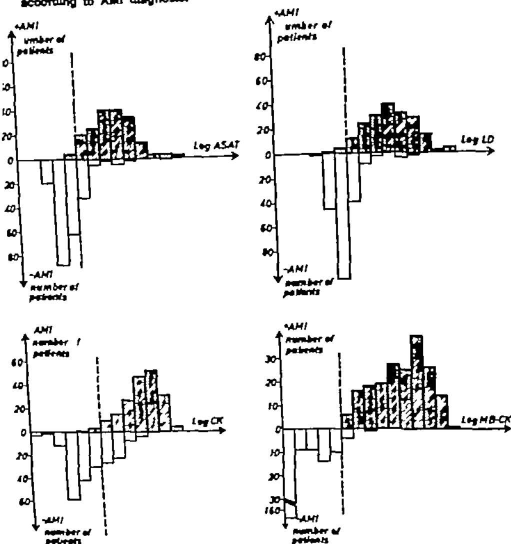
In a consecutive series of 401 patients admitted to the Coronary Care Unit of the Copenhagen County Hospital at Glostrup suspected of acute myocardial infarction (AMI) less than 24 hours old, blood samples for enzyme analysis were drawn at admission and 12, 24 36, 48 and 72 hours later and ECG in 9 leads was recorded daily during the first week. From usual diagnostic criteria — clinical symptoms, ECG-findings, and enzyme analyses, not including and not knowing the results of CK—MB analyses — the series was divided into patients with AMI and those without AMI

Comparison is made between the predictive values in the diagnosis of AMI of a positive and a negative result (PV pos. and PV-neg) of either of the tests ECG and serum levels of aspartate aminotransferase (ASAT) lactate dehydrogenase (LD) creatine kinase (CK) and MB-fraction of CK determined by electrophoresis. The salient features were PV neg. i.e diagnostic sensitivity was low (0.78) for ECG but high for all enzyme tests (0 97—1 00) PV-pos. i e diagnostic specificity was rather low for the three standard enzymes (0.73—0 87) but high for CK—MB (0 98) and also for ECG (1 00) Thus, determination of CK—MB seems to offer the best combination of a high sensitivity as well as specificity in the diagnosis of AMI However the time factor should be kept in mind as positive results of CK—MB can only be expected during the first 30—50 hours after the onset of the AMI.

The early and reliable identification of acute myocardial infarction (AMI) is a common and important clinical challenge. The detection of rising blood levels of certain enzymes known to be released from an infarcted myocardium has become an essential part of this clinical diagnosis. However the enzyme tests now in general use in the diagnosis of AMI — the aspartate aminotransferase (ASAT) the lactate dehydrogenase (LD), and the creatine kinase (CK) — apparently show only a limited specificity for the purpose and the number of false positive results in these patients are probably rather consistent (1 10)

The separation of the CK into the three isoenzymes, MM MB, and BB, seems to offer possibilities for significantly increasing the specificity of the test (4 6, 8) Analyses of tissue extracts indicate that the isoenzyme CK—MB is found only in the myocardium in amounts sufficient to cause significant increase in serum concentration (2, 4 6 14) The clinical experience from a large group of patients, reported below seems to confirm the presumption that determination of CK—MB levels is the hitherto most specific and sensitive diagnostic test for a fresh AMI

Fig 1
Frequency distribution of ASAT LD CK, and MB—CK in 401 patients grouped according to AMI diagnosis.



Patients and methods

Patients

Criteria for entering the study were: (1) Clinical suspicion of AMI begun less than 24 hours before admission, and (2) availability of three assays with 12 hours interval of each of the enzyme tests within their respecti diagnostic period LD 12—96 hours, ASAT and CK 6—60 hours, and CK—MB 6—48 hours after the onset of symptoms.

During period of 6 months (October 1976—March 1977) 466 patients were admitted to the Coronary Care Unit of the Copenhagen County Hospital in Glostrup with the suspicion of an AMI less than 24 hours old.

Predictive values of negative and positive outcomes of enzyme analyses and of ECG in 401 patients of whom 192 had AMI.

Results	Predictive value				
	CK—MB	CK	ASAT	LD	ECG
Negative	1 00	0 98	0 97	0 98	0.78
Positive	0 93	0.73	0 87	0.77	1 00

In 45 of those patients, data collection did not fulfill the criteria, as 8 paients died and 37 were discharged before sufficient data were obtained In another 20, the diagnosis AMI could *not* be *definitely established.*

The remaining 401 patients were classified into one of two groups. One of 192 patients (146 men and 46 women, age 36—88 years, mean 62 2 years) fulfilled the criteria for the diagnosis AMI The second group of 209 patients (140 men and 69 women, age 36—90 mean 59 8 years) did not meet the same criteria.

Methods

The diagnosis AMI was made in accordance with the criteria suggested by WHO (16) thus comprising clinical symptoms, ECG findings, and results of ASAT LD and CK, but not regarding the results of the CK—MB analysis.

ECG in 3 bipolar extremity and 6 unipolar precordial leads was recorded daily during the first 5 days and at least once a week for the subsequent period.

Blood samples were drawn immediately after admission and subsequently about 12 24 36 48 and 72 hours later All enzyme analyses were made from unhemolysed serum, according to the recommended methods (11 12) Rate measurements for the kinetic methods were made at 37 C with an LKB 8600 reaction rate analyser and an Hitachi Perkin-Elmer recorder

CK—MB determinations were performed by electrophoresis on agarose gel and quantification by fluorescense scanning (3)

Calculation of the results

The result of each test parameter was considered separately and without knowledge of the other The enzymatic parameters were considered pathological if at least one of the respective assays showed activity above the upper discriminative limit. ECG was evaluated in accordance with the WHO recommendations (16)

To make a clear comparison of the test parameters, the predictability was calculated as follows The predictability of positive test (PV pos) = the number of patients diagnosed as AMI showing pathological parameters divided by the total number of patients with a pathological test result. The predictability of a negative test (PV neg) = the number of patients without AMI showing non-pathological test parameters divided by the total number of subjects with a negative test result. The efficacy of a test is defined as the sum of true positive and true negative results divided by the total number of tests performed.

Results

The figure gives the frequency distribution of ASAT LD CK, and CK—MB The discriminative limit is indicated by the dotted line The limit is placed with the object of avoiding false negative results rather than false positive ones.

The above table lists the predictive value of each test parameter The predictive value of of negative test demonstrate almost identical results for all *four* enzymatic assays. ECG however shows a *significantly lower*

PV-neg., i.e. a low diagnostic sensitivity in 61 out of the 192 patients diagnosed as AMI, the ECG showed no characteristic infarct pattern, usually due to the presence of bundle branch block or sequelae of previous AMI. The alues of PV-pos. demonst rate that, in diagnostic specificity charac teristic electrocardiogram and a pathological CK—MB are superior to the standard enzyme results. The efficacy based on the indicated discriminative limits is as follows ASAT 0.90 LD 0.85 CK 0.83 CK—MB 0.99 and ECG 0.85

Discussion

The value of any new test must rest on comparisons with the known ad antages and disadvantages of existing test, and its application to common use should depend on convincing evidence of its superiority

In the diagnostic procedure of AMI, there is little doubt that serum enzyme have been clinically useful and important. In clinical routine, emphasis has usually been placed on serial enzyme studies because of the generally low specificity of most enzymes applied in this connection. Thus, CK can be elevated by intramuscular injections, lung disease, cerebrovascular disease, convulsions, chronic alcoholism (5), and strenuous exercise (13)

I the evaluation of a diagnostic test such CK—MB, major problem is the lack of control diagnostic procedure. Autopsic data will be available only in a minority and generally the tested parameter will be part of the diagnostic criteria against which t is tested. In our series, CK—MB analyses w kept out of the diagnostic criteria, thus probably slightly improving the specificity of the other three enzymes compared with that of the CK—MB.

Apart from its alue in the qualitative diagnosis of AMI, serial enzyme determination might also gi e a good picture of the inf rct size and provide useful prognostic index (9) and lso measure of the effect of any attempt to restrict the extension of infarction (7).

The frequency distribution, as presented in Fig. 1 shows a varying degree of over lapping between the activity areas in whom patients with and those without AMI will be found. The frequency of false positive and false negative results is determined by the position of the discriminative limit, i.e. the vertical dotted line placed according to clinical considerations. The best possible test parameter will be the one that shows a frequency distribution whose area of overlapping is smallest. None of the four distributions ar perfect, but CK—MB is obviously considerably better than the others.

The predictability is estimated from the point of view that in the practical use of a diagnostic test, the likelihood of a disease being present when a test esult is pathological, or absent when a test result is normal, is generally preferable to the reverse state of affairs the likelihood that, in a sick person the test is pathological, and in nor mal person the test shows a normal result (15 17).

From the table, t is evident that CK—MB has the highest diagnostic sensitivity (PV-neg) and a diagnostic specificity (PV pos.) almost as high as that of the ECG This suggests that a pathological test result of the CK—MB or the ECG is almost diagnostic of AMI. On the other hand, failure to demonstrate pathological serum enzyme levels within the diagnostic period in the case of ASAT LD and CK is strongly suggestive, and in the case of CK—MB presumably safe evidence, that AMI is not present. However due regard must be paid to the time factor After more than 30—50 hours after the supposed time of onset of AMI the course of standard enzymes is usually more relevant to the diagnosis than are the values of CK—MB

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Serial CPK determinations after acute myocardial infarction The possible use of this technique in objective evaluation of myocardial infarction treatment.

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Serial serum CPK determination during the first hour after the initial elevation of enzyme activity following acute myocardial nfarction can be used to ompute the further development in serum CPK activity and to predict the infarct size in experimental dog studies and in patients with acute myocardial infarction (2, 3) However in patients, the prediction in single individual is only valid if the infarction is sudden and definite, similar to the experimental model, which applies to approximately 30 per cent of the patients (1) I patients with re-infarction or with gradual progression of the necrotic area, the prediction fails (1)

The method of serial CPK determinations has lso been used to study the effect of treatment that might protect jeopardized ischaemic myocardial cell from necrosis (2, 3 4) So far the esults of reperfusion by release of constricting oronary artery cuff in dogs, the administration of propranolol to dogs, and the administration of trimetaphane in hypertensi humans ha been eported.

I these reports, the curve of serial CPK determinations given shows raped and dr stic f ll in CPK activity following the treatment. If this fall reflects salutary effect of the tr atment, it provides simple method for appraising the ability of different kinds of treatment to limiting the extent of myoca dial ell necrosis Complicated mathema tical calculations would be unnecessary – observations of drop in CPK activity would indicate beneficial effect. The present work studied whether such a visible drop in the serum CPK level could be obtained after "myocardial protection treatment"

Material and methods

Five patients with acute myocardial infarc tion were given 5 mg of propranolol intravenously for 5 minutes, and 3 patients were treated with intravenous infusion of phentolamine for 3—4 hours. The serum CPK activity was determined in blood samples obtained at $^1/_2$—2-hourly intervals. The treatment was initiated 5—17 hours after the onset of chest pains.

Results

Fig. 1 and 2 show the results. The treatment did not produce drop in the serum CPK activity in any patient. This observation agrees with the clinical impression The patients did not benefit from the treatment. W therefore ref ained from further experiments.

Comments

The rather disappointing results led us to scrutinize the above-mentioned presented curves (2, 3 4) It is rather bewildering that the drop in CPK activity shown is far greater than the decay rate Even if all the cells, both the jeopardized ones and the irreversibly damaged, immediately ceased to release CPK, the slope of the curve would

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The predictive value of myocardial scintigraphy with ^{99m}technetium pyrophosphate in diagnosing acute myocardial infarction

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Abstract

Myocardial scintigraphy with ^{99m}technetium-pyrophosphate was performed in two selected groups of patients, consisting of 20 who had acute myocardial infarction (AMI) clinically and 18 who had no AMI clinically. The purpose was to estimate the value of this method in the detection or disproof of AMI compared with usual procedures (ECG and serum enzyme determination — GO-transaminase and α_1-fraction of LDH).

Each of the 20 patients with clinical AMI had positive scintigrams. There were no false negative findings. Out of 18 without AMI, 15 had negative scintigrams in the other 3 scintigraphic findings were false-positive.

The prevalence of AMI among patients admitted to the cardiological department was 0.39 1 this population of patients, the calcul ted predictive alue of a positive scintigram was 0.80 whereas the predictive alue of a negative was 1.0. In patients admitted to the coronary care unit, the prevalence of AMI was 0.51 the corresponding predictive alues of positive scintigram was 0.86 and of a negative 1.0

The identity between scintigraphic and lectrocardiographic infarct localization was good. Infarct size estimated by scintigraphy was not significantly correlated to the maximum elevation of serum enzyme concentr tion.

In patients suspected of having AMI, it is highly probable that negative scintigram obtained f om day 2 to day 6 after the onset of symptom will rule out the presence of acute myocardial infarction.

Introduction

The diagnosis of acute myocardial infarction (AMI) based on the occurrence of chest pain, sequential electrocardiographic changes, and elevation of serum enzyme activity cannot always be made with certainty. In recent years, the search for safer method for detecting or excluding the presence of AMI has led to the use of isotope scintigraphic technique for visualizing the infarcted area of the myocardium (2, 3 9)

The purpose of this study was to determine the predictive value of a positive and a negative myocardial scintigram.

Material and methods

20 patients with and 20 patients without clinical AMI were investigated. The diagnosis was based on the simultaneous presence of two of the following three phenomena typical history of disease, characteristic ECG-changes, and temporary elevation of serum enzyme activity (serum aspartateaminotransferase [ASAT] and α_1 fraction of serum-lactatedehydrogenase [LDH] Fourteen patients in the group with AMI had transmural infarction, 2 had non-penetrating (non transmural) infarction, 3 had subendocardial infarction, and one had left bundle branch

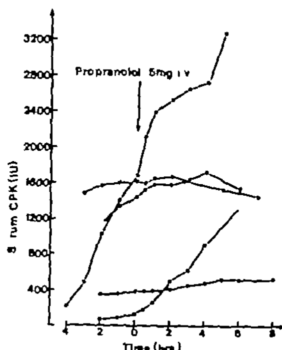


Fig 1 Serial CPK determinations in 5 patients with acute myocardial infarction treated with 5 mg of propranolol i. v

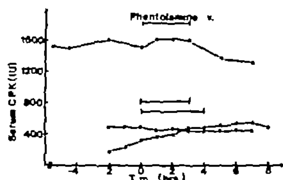


Fig 2 Serial CPK determinations in 3 patient with acute myocardial infarction treated with phentolamine (0 15—0 2 mg/min).

not be as steep as presented. This puzzling problem makes us doubt the use of serial CPK determinations as an indication of myocardial cell protection The rapid fall in CPK activity seems to represent an artefact caused by the intervention.

It might be argued against our results that the treatment was given rather late in the course of the infarction when most of the irreversible damage is probably already done A lack of effect during this stage is not surprising However the same argument can be presented against previously reported studies in patients in whom the treatment was started about 13 hours after the onset of chest pains. None the less, a reduction of infarct size from 53 CPK gramme equivalent to 27 was obtained after trimetaphane treatment in a hypertensive patient. It is difficult to understand that the effect of treatment can be so extensive at this stage.

Recently the reservation was made that the evaluation of treatment can only be performed in groups of patients and not in the individual (5) However until the drastic fall in serum CPK activity is explained the applicability of the method must be questioned even when used in groups of patients.

This presentation was not primarily intended to submit our own observations, but to find an opportunity to pinpoint previously published results that could be mislead ing

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Fig. 2. Positive (4+) scintigrams of patient with extensive acute anterior wall infarction shown in A) anterior B) 45° left anterior oblique C) left lateral views.



Fig. 3. Positive scintigrams of patient with acute infero-lateral infarction shown in A) anterior B) 45° left anterior oblique C) left lateral views.

the 18 without clinical AMI had negative scintigram scintigraphic findings were positive the remaining three. Nosographically this meant that the probability of a positive scintigram in patients with AMI was $\frac{20}{20}$ =1.0, whereas the probability of a negative scintigram in those without AMI wa $\frac{15}{18}$ =0.83

The diagnostic probabilities were calculated with Bayes theorem (14). The pre lence of AMI among patients admitted to the cardiological department in Hvidovre hospital was 0.39. The corresponding predic tiv alue of positiv scintigram was 0.80, and that of negativ scintigram wa 1.0

Table I. Scintigraphic compared with clinical diagnosis.

		SCINTIGRAPHY	
		+	—
AMI	+	20	0
	—	3	15

I patients admitted to the coronary care unit in Hvidovr hospital, the prevalence of AMI was 0.51. The corresponding figure for the predictive lue of a positiv scintigram was 0.86 and for a negative, 1.0.

block, which made judgement of the ECG impossible.

Two were excluded from the control group of patients without clinical AMI One because she had streptococcus endocarditis The other because he had earlier had myocardial infarction.

Informed consent was obtained from each patient on entering the study

The investigation was made with a gamma camera with high resolution collimator collection 500 000 counts one hour after the intravenous injection of 15 mCi ^{99m}Tc pyrophosphate (Tc PYP) Pictures were obtained in the anterior (AP) the left anterior oblique (LAO) and the left lateral (LL) projections

The scintigrams were evaluated jointly by two investigators without previous knowledge of the clinical diagnosis. The degree of intensity of myocardial uptake was graded according to an arbitrary scale described by Parkery et al (8) 0 (no activity) 1+ (questionable activity) 2+ (definite activity) 3+ and 4+ (increasing degrees of activity within the infarct zone) Zero and 1+ were considered negative 2+ 3+ and 4+ *in only one projection were considered positive.* Infarct localizations were estimated as anteroseptal antero-apical antero-lateral and inferior or combinations of these.

Infarct size was estimated as follows small (smaller than the width of 2 ribs with interjacent intercostal space) medium (corresponding to the width of 2 ribs) large (larger than the width of 2 ribs)

Electrocardiographic infarct localization was defined as follows antero-septal (V_{1-3}) antero-apical (V_{3-5}) antero-lateral (V_{4-6}, AVL, I) inferior (II III and AVF)

Results

Figure 1A—C shows a normal (negative) scintigram of a patient without clinical evidence of AMI

Figure 2A—C demonstrates typical scintigrams in three projections from a patient with AMI Note typical doughnut or horse shoe appearance of increased myocardial uptake surrounding central area with sparse activity

Figure 3A—C demonstrates an inferior infarction characterized by a disclike activity in the diaphragmatic wall Being viewed from the side in all three projections, the infarct size cannot be estimated and a central decrease in activity cannot be observed In the patients with AMI scintigraphy was performed within day 1 to day 6 of observation (mean 3 0 days) Each of the 20 patients had a positive scintigram (Table I) Fifteen of



Fig 1 Negative (normal) myocardial scintigrams of a patient without acute myocardial infarction shown in the three standard views A) anterior B) 45° left anterior oblique C) left lateral Note activity in the sternum in the middle of A) and to the left in B) and activity in the vertebral column behind ribs in the middle of B) and to the right in C).



Fig 2. Positive (4+) scintigrams of patient with extensive acute anterior wall infarction shown in A) anterior B) 45° left anterior oblique C) left lateral views.



Fig 3 Positive scintigrams of patient with acute infero-lateral infarction shown in A) anterior B) 45° left anterior oblique C) left lateral views

the 18 without clinical AMI had negative scintigram scintigr phic findings were positive the remaining three. Nosographically this meant that the probabil ty of positive scintigram in patients with AMI w $\frac{20}{20}$ =1.0, whereas the probability of negative scintigram in those without AMI was $\frac{15}{18}$ =0.83

The diagnostic probabilities were calculated with Bayes theorem (14) The prevalence of AMI among patients admitted to the cardiological department in Hvidovre hospital w 0.39 The corresponding predic ti e alue of positive scintigram was 0.80, and that of negati e scintigram was 1.0.

T ble I Scintigraphic compared with clinical diagnosis.

		SCINTIGRAPHY	
		+	—
AMI	+	20	0
	—	3	15

In patients admitted to the coronary care unit in Hvidovre hospital, the prevalence of AMI w 0.51 The corresponding figure for the predicti value f positi e scintigram was 0 86 and for negati 1.0.

Table II Scintigraphic compared with electrocardiographic infarct localization

		SCINTIGRAPHY	
		Anterior	Inferior
ECG	Anterior	13 *)	—
	Inferior	—	7

*) 1 patient had left bundle branch block

Scintigraphic infarct size was not significantly correlated to the maximum elevation of serum enzyme activity in patients with AMI

In the group of patients with clinical AMI 7 had inferior infarction on both scintigram and electrocardiogram 13 showed an anterior infarction on the scintigram and 12 of them had corresponding electrocardiographic localization. The other patient had left bundle branch block that did not permit determination of infact localization, but autopsy one week later revealed recent infarction in the anterior wall of the left ventricle.

Table III gives a comparison of scintigraphic and electrocardiographic subdivisions of anterior wall infarctions.

Our material did not contain either electrocardiographic or scintigraphic posterior infarctions.

Discussion

Since 1974 ^{99m}Tc labelled radiopharmaceuticals which sequester in acutely infarcted myocardium have been used clinically for positive scintigraphic visualization of AMI Among several compounds, the bone-seeking technetium phosphates have gained the greatest popularity In animals, they concentrate in infarcted myocardial tissue with an infarct/normal myocardium ratio of about 10 (2) It was recently shown (4) that Tc PYP is superior to both ^{99m}Tc tetracycline and ^{99m}Tc-glucoheptonate in detecting acute myocardial infarction.

The mechanism of uptake in infarcted, and possibly severely ischaemic, myocardial tissue is not known with certainty A certain perfusion is necessary for the tracers to reach their target (7 9) and they are likely to localize primarily in the border zone of the infarcted area. Necrotic myocardial cells accumulate calcium ions. These are probably bound in hydroxyapatite like structures that have been observed in infarcted and perhaps also in ischaemic myocardial cells (3 8 9 10)

We found a positive scintigram in each

Table III Anterior infarct localization Thirty four scintigraphic localizations compared with 32 electrocardiographic localizations.

		SCINTYGRAPHY			
		Antero-septal	Antero-apical	Antero-lateral	Undetected
ECG	Antero-septal	8			2
	Antero-apical		12		
	Antero-lateral	1		7	2
	Undetected		2	4	

of the 20 patients with clinical AMI. This corresponds to the findings of other investigators, who have no false negative scintigrams with Tc-PYP where myocardial scintigraphy was carried out from 18 hours to 6 days after the onset of symptoms. The false-positive scintigrams that we found might be due to insufficient selection of the control group. On the other hand, some patients w th heart aneurism (1 6) and unstable angina (13) have been reported to demonstrate positive scintigrams in the *absence of clinical* evidence of AMI. False-positive scintigrams ha e also been described in patients after left radical mastectomy in a patient with carcinoma of the left lung treated with X rays (11) and in an instance of secondary hyperparathyreoidism with complicating uraemic pericarditis (5)

In patients with AMI positive scintigrams with T-PYP and other bone-seeking technetium labelled phosphates will become negative within one or tw weeks after the onset of symptoms, unless left ventricular aneurism or akinesis develops. The use of Tc PYP after this period makes the demonstration of repeated infarcts possible With ^{99m}Tc tetracycline and ^{201}thallium, scintigrams will be positive in patients with old infarctions.

In our investigation, t was possible to distinguish between anterior and inferior infarctions (Table II) It was also possible to estimate the localization and extention of anterior infarctions with satisfactory accuracy (Tabl III) Two antero-septal localizations were overlooked on the scintigrams undoubtedly accumulation of activity in the sternum made interpretation difficult. In tw patients, scintigrams did not reveal an antero-lateral localization which was registered lectrocardiographically One of these patients had a subendocardial infarction with rather faint and diffuse accumulation of activity whereas the other had an inferior infarction both electrocardiographically and scintigr phically but ECG also showed changes in lead V_6. Conversely 4 antero-lateral and 2 antero-apical inf rct localizations that were not seen on the ECG were described on the scintigrams. In these cases, scintigraphy overestimated the extent of infarction, indicating that Tc-PYP might not only mark necrotic myocardial tissue, but possibly also severely ischaemic myocardial cells, as has been shown experimentally in animals (7)

In one patient with electrocardiographical inferior and antero-lateral infarct, the scintigraphic localization was inferior and antero-septal. Here too, the explanation might be labelling of ischaemic cells, because shortly afterwards the patient developed antero-septal infarction that was later verified at autopsy

The method is not specific, but applied to patients admitted to coronary care unit with suspicion of AMI, the predictive value of a positive scintigram was reasonably high (0.86) Naturally this information has limited value, because the scintigraphic method was compared with other investigations (ECG and serum enzyme activity) whose diagnostic value is not definitely known. However in patients with AMI, the scintigrams almost always seem to be positive on the second or third day after the onset of symptoms. Combined with a predictive alue of a negative scintigram of 1.0, this implies that a negative scintigram obtained on the third day of observation can exclude with considerable certainty the presence of AMI (defined according to current criteria)

In conclusion, we find that the method has its most important diagnostic values where the electrocardiogram might fail to disclose an acute myocardial infarction in patients with bundle branch block, ld myocardial infarction, or subendocardial infarction (12) Our investigation showed that a negative myocardial scintigram will rule out the presence of AMI with a high degree of probabil ty Time will show whether the method will gain additional importance in the early detection of postinfarction aneurisms, in estimating the infarct size, particularly during infarct-limiting treatment, and hope f lly become useful tool for a better understanding of the pathophysiology of acute myocardial infarction.

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The variability of ST segment in the early phase of acute myocardial infarction

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Abstract

The ST segment elevation was measured hourly via single surface unipolar lead for 48 hours after admission, in 30 patient with acute myocardial infarction (AMI) admitted, on average 2 hours after the onset of symptoms. In 14 patients with anterior AMI the recordings were made through the precordial lead that initially showed the maximum ST elevation. In 16 patients with inferior AMI, the aVF lead was used. Twenty-five control patients without AMI had the ST deviation measured hourly for 24 hours 15 of them had the recording made via the V4, aVF being used with the others. Our data for the reliability of the method showed that the variations in ST deviations in the control group were of the same magnitude as those observed with the measuring error of the method itself

The investigation showed that the spontaneous course of the hourly measured ST elevations in the early phase of AMI was marked by pronounced variability and that this applied to both anterior and inferior infarctions. The intra-individual patient variation of the ST elevation was significantly greater than in the control group of patients. The inter-individual patient variation of the ST elevation with AMI was also significant. The ST elevation was correlated to heart rate mean arterial blood pressure, heart rate multiplied by systolic blood pressure, and respiratory rate and it could be shown partly that there was a significant dispersion of the correlation coefficients within the separate correlation groups, and partly that the correlation coefficients were variable between the groups. It was also shown that nasal oxygen therapy and cardiac pain had no bearing on ST elevation. The variability of ST elevation was thus most often inexplicable and only rarely accounted for by alterations in the clinical status.

It is generally accepted that ST segment elevation in the ECG is one of the characteristic features of acute myocardial infarction (AMI) but the electrophysiological basis of changes in the ST segment in myocardial ischaemia has not been completely clarified (1)

In recent years, several investigations have been carried out where ST elevation has been used as a quantitative indicator of myocardial ischaemia. With multiple leads and epicardial and precordial mapping techniques, the sum of ST elevations has been used as an estimate of the extent of ischaemic injury after coronary occlusion in animal and after AMI in man (7 8 9 12, 13) However from the theoretical and experimental bases of ST segment deviation, it has been suggested that ST segment mapping is not reliable measure of myocardial ischaemia (4 5) Other investigators have pointed out the limitations

of this method when used for the bedside estimate of ischaemic injury (11 15)

These studies suggest that there is a con siderable variability of the ST deviation after AMI Therefore, in an attempt to elu cidate this problem we have studied the ST elevation from hour to hour in a single sur face lead for the first 2 days after admission of patients with AMI and have related the ST elevation to ST deviations measured hourly in patients without AMI In addition, the ST elevations in patients with AMI have been related to heart rate blood pressure, respiratory rate, retrosternal pain and oxygen treatment clinical factors that can be asso-ciated with or can influence, myocardial ischaemia.

Material and method

1 The patient group

The investigation includes 30 patients with AMI admitted to the coronary care unit (CCU) of the Odense University hospital, on average 2 hours after the onset of symptoms. Their average age was 63 years There were 22 men and 8 women Patients with pericarditis, disturbances of electrolyte ba lance, a QRS duration $\geq 0\ 12$ seconds, or patients under drug therapy possibly affect ing the ST segment (digitalis, isoproterenol beta adrenergic blocking drugs) were not admitted to the study

The patients were treated according to the usual procedure of the CCU i e. rest in bed, morphine, anti arrhythmic drugs, and diure tics as required and oxygen via a nasal catheter when considered necessary usually 2—6 l/min. However if treatment with digoxin, isoproterenol glucagon, beta adren ergic blocking agents, or verapamil was in-stituted during the period under study mea surement of the ST elevation was discon tinued. Should a QRS duration of $>0\ 12$ seconds or pericarditis occur then the values of the ST elevation were excluded from this point in the final analysis.

Stethoscopy of the lungs and heart was frequently carried out during the period under study If stethoscopy suggested con gestive heart failure then a chest X ray was taken. In accordance with clinical arbitrary classification of congestive heart failure in patients with AMI (2) 2 patients had no signs of cardiac failure, 25 patients had mild to moderate heart failure, with rales of both lung fields of 50 per cent or less, and 3 had pulmonary oedema with rales over more than 50 per cent of both lung fields. No patients suffered from cardiogenic shock.

All the patients complained of retrosternal pain for more than 20 minutes. Based on this and also on the daily routine recordings of an ECG with 12 leads (I—III aVR, aVL, aVF V_1—V_6) together with the daily deter mination of creatine kinase, aspartate amino-transferase, and lactate dehydrogenase in the serum, a definite diagnosis of AMI was made according to the criteria of WHO (16) Fourteen patients had anterior infarction, whereas 16 had inferior infarction.

2 ECG recording and measurement

In patients where the initial ECG recording showed an ST elevation ≥ 2 mm in V_1—V_6. 42 sites were marked on the front of the chest. These sites were obtained by the crossing of 6 horizontal lines and 7 vertical lines. The horizontal lines were fixed by permitting line A to cut IC II at the stern um and line B, IC III at the sternum. The vertical distance between lines A and B was measured, and was used for the positioning of lines, C, D E, and F in a distal sequence With regard to the vertical lines, lines 1 and 2 were drawn along the right and left sternal borders, respectively and lines 6 and 7 in the left anterior and middle axillary line, respectively Lines 3 4 and 5 were obtained by dividing the distance from lines 2 to 6 by four An ECG was recorded at these 42 sites and an electrode (Red Dot silver/silver chloride) attached to the chest at the site with the highest ST elevation. An ECG was then recorded using this electrode, every hour for the next 48 hours.

In patients where the initial ECG record ing showed the highest ST elevation in III and aVF (≥ 1 mm) ECG recordings were made every hour for the next 48 hours using

the lead aVF. All the ECG recordings were made with the patient in the supine position.

The electrocardiograph was a Siemens Elema Mingograph 34 with a paper speed of 50 mm/sec and calibrated to 1 mV = 10 mm. The ECG complex was analysed by means of Hewlett Packard 9864A digitizer/9810A calculator. The digitizer consists of three elements: a platen with a digitizing surface, a free moving cursor and a main frame. It enters co-ordinate data from graphic records into a calculator. The duration of the QRS complex and the height of the ST segment 0.06 seconds after the peak of the last wave (usually the S wave in the QRS complex) were calculated with 3 consecutive ECG complexes; using these 3 adjacent intervals, we calculated the heart rate as the harmonic mean. The PQ level was used as the base line.

The blood pressure and respiratory rate were measured at the same time as the ECG was recorded. The blood pressure was measured indirectly with a cuff sphygmomanometer and read to the nearest 5 mm Hg.

3 *The control group*

Twenty-five patients comprised the control group; of these, 20 were admitted for chest pain but with no indication of AMI and 5 because of extracardiac disease. The average age of the control patients was 49 years; there were 18 men and 7 women. The final diagnoses of these patients were: pneumonia 5, ischaemic heart disease 4 (no retrosternal pain or discomfort during the period under study), intercostal muscle myoses 3, diabetes mellitus 2, cholelithiasis 2, lipothymia 2. Two other patients had no definite diagnosis; the remaining 5 patients suffered from neurosis cordis, arterial hypertension, influenza, migraine, and an electric accident, respectively. An ECG was recorded every hour in each of these patients, but for 24 hours only as described in the paragraph on the patient group. Fifteen patients comprised the control group for the patients suffering from anterior infarction, and the ECG was recorded from a precordial lead corresponding to V_3. In the remaining 10 control patients for those with an inferior infarction the aVF lead was employed for the recording.

4 *Reliability of the measurements*

The precision of the measurement of length on the scale of the digitizer was checked by measuring a 5 cm length twenty times leaving the paper in the same position on the platen throughout, and then for a further twenty times, but removing and replacing the paper between each measurement.

The *intra-observer variation in the measurement of the ST deviation* by means of the digitizer was studied by twice measuring twenty ST deviations, registered in a precordial lead from the same patient with anterior AMI, at an interval of 24 hours.

The *inter-observer variation in the measurement of the ST deviation* was also studied by having another person (using the same digitizer) measuring the same twenty ST deviations.

The *influence of the electrocardiograph on the measurement of the ST deviation*, was studied by means of two Mingographs 34. An ECG was recorded by both instruments, one immediately after the other using a precordial lead on 10 patients. The examination was repeated on each patient.

The *influence of different patient positions on ST deviation* was evaluated by ECG recordings immediately following each other with the patient first in the left oblique position, second in the supine position, and finally in the right oblique position. This procedure was repeated with each patient, an ECG recording being made via a precordial lead; this was carried out on 10 patients (6 controls and 4 with anterior AMI).

5 *Statistical analysis*

The formula

$$PSD^2 = \frac{\sum_{i=1}^{k} df_i \times SD_i^2}{\sum_{i=1}^{k} df_i}$$

was used for the calculation of the pooled variance of ST deviations in the control group and also for the calculation of the total pooled variance when evaluating the precision of the

of this method when used for the bedside estimate of ischaemic injury (11 15)

These studies suggest that there is a considerable variability of the ST deviation after AMI Therefore, in an attempt to elucidate this problem, we have studied the ST elevation from hour to hour in a single surface lead for the first 2 days after admission of patients with AMI and have related the ST elevation to ST deviations measured hourly in patients without AMI In addition, the ST elevations in patients with AMI have been related to heart rate, blood pressure, respiratory rate, retrosternal pain and oxygen treatment clinical factors that can be associated with, or can influence, myocardial ischaemia

Material and method

1 The patient group

The investigation includes 30 patients with AMI admitted to the coronary care unit (CCU) of the Odense University hospital on average, 2 hours after the onset of symptoms. Their average age was 63 years. There were 22 men and 8 women. Patients with pericarditis, disturbances of electrolyte balance, a QRS duration ≥ 0.12 seconds, or patients under drug therapy possibly affecting the ST segment (digitalis, isoproterenol, beta adrenergic blocking drugs) were not admitted to the study

The patients were treated according to the usual procedure of the CCU i.e. rest in bed, morphine, anti arrhythmic drugs, and diuretics as required, and oxygen via a nasal catheter when considered necessary usually 2—6 l/min. However if treatment with digoxin isoproterenol, glucagon, beta-adrenergic blocking agents, or verapamil was instituted during the period under study measurement of the ST elevation was discontinued. Should a QRS duration of >0.12 seconds or pericarditis occur then the values of the ST elevation were excluded from this point in the final analysis.

Stethoscopy of the lungs and heart was frequently carried out during the period under study If stethoscopy suggested congestive heart failure, then a chest X-ray was taken. In accordance with clinical arbitrary classification of congestive heart failure in patients with AMI (2) 2 patients had no signs of cardiac failure, 25 patients had mild to moderate heart failure, with rales of both lung fields of 50 per cent or less, and 3 had pulmonary oedema with rales over more than 50 per cent of both lung fields. No patients suffered from cardiogenic shock.

All the patients complained of retrosternal pain for more than 20 minutes. Based on this and also on the daily routine recordings of an ECG with 12 leads (I—III aVR, aVL, aVF V_1—V_6) together with the daily determination of creatine kinase, aspartate aminotransferase, and lactate dehydrogenase in the serum, a definite diagnosis of AMI was made according to the criteria of WHO (16) Fourteen patients had anterior infarction, whereas 16 had inferior infarction.

2 ECG recording and measurement

In patients where the initial ECG recording showed an ST elevation ≥ 2 mm in V_1—V_6, 42 sites were marked on the front of the chest. These sites were obtained by the crossing of 6 horizontal lines and 7 vertical lines. The horizontal lines were fixed by permitting line A to cut IC II at the sternum and line B, IC III at the sternum. The vertical distance between lines A and B was measured, and was used for the positioning of lines, C, D E, and F in a distal sequence. With regard to the vertical lines, lines 1 and 2 were drawn along the right and left sternal borders, respectively and lines 6 and 7 in the left anterior and middle axillary line, respectively Lines 3 4 and 5 were obtained by dividing the distance from lines 2 to 6 by four An ECG was recorded at these 42 sites and an electrode (Red Dot silver/silver chloride) attached to the chest at the site with the highest ST elevation. An ECG was then recorded using this electrode, every hour for the next 48 hours.

In patients where the initial ECG recording showed the highest ST elevation in III and aVF (≥ 1 mm) ECG recordings were made every hour for the next 48 hours using

the lead aVF All the ECG recordings were made with the patient in the supine position.

The electrocardiograph was a Siemens-Elema Mingograph 34 with a paper speed of 50 mm/sec and calibrated to 1 mV= 10 mm. The ECG complex was analysed by means of a Hewlett Packard 9864A digitiz er/9810A calculator The digitizer consists of three elements platen with a digitizing surface, free moving cursor and a main frame; it enters co-ordinate data from gra phic records into a calculator The duration of the QRS complex and the height of the ST segment 0.06 seconds after the peak of the last wave usually the S wave in the QRS complex, were calculated with 3 consecutive ECG complexes, using these 3 adjacent inter vals, we calculated the heart rate as the har monic mean. The PQ level was used as the base line.

The blood pressure and respiratory rate were measured at the same time as the ECG was recorded. The blood pressure was measured indirectly with cuff sphygmomanometer and read to the nearest 5 mm Hg

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In patients where the initial ECG recording showed the highest *ST elevation in III and aVF* (≥1 *mm*) ECG recordings were made every hour for the next 48 hours using

precordial lead was attached. In all the patients, the initial highest ST elevation was measured in the antero-septal area. The first measurement of the ST elevation was carried out 357 $\pm$ 47 minutes (mean $\pm$ SEM; range 150—610 min) after the onset of the infarction. The table also shows the variances of the hourly measurements of the ST elevations in each individual patient. A comparison was made between these values and the pooled variance of the ST deviation of the control group in order to evaluate the intra-individual variation, and by means of a F-test, it was found that 13 of the 14 patients had a significantly increased variance in relation to the patients of the control group. Patients Nos. 3, 8 and 33 died, 91/10, and 41 hours, respectively after the onset of symptoms. Thirteen measurements of the ST elevation only are given in the table for patient No. 12, the reason for this being that the patient developed a QRS > 0.12 seconds.

The first measurement of ST elevation in lead aVF was carried out 155 $\pm$ 21 minutes

Table II Electrode position and intra-individual variation of ST elevation in patients suffering from anterior AMI

Case no.	Electrode position	N of measurements	Variance of ST elevation (Pooled 0.067)	Significance
3	C3	8	0.303	P<0.01
5	C2	48	4.068	P<0.01
7	E3	50	0.978	P<0.01
8	E3	5	0.373	P<0.01
11	D2	48	0.279	P<0.01
12	D2	13	1.435	P<0.01
14	E2	51	0.063	n.s.
21	C3	49	0.995	P<0.01
22	D	51	0.243	P<0.01
23	C3	57	0.353	P<0.01
29	C2	48	0.813	P<0.01
31	C2	50	0.741	P<0.01
33	C3	36	0.608	P<0.01
37	D3	50	0.116	P<0.01

The pooled variance is from 15 control patients

(mean $\pm$ SEM range 30—355 min) after the onset of symptoms in 16 patients with inferior AMI. With a F test comparison of the individual patient's variance of the hourly ST elevation, with the pooled variance of the ST deviation of the 10 control patients, showed that 15 of the 16 patients had a significantly increased variance. In patient No. 10, only 6 measurements of the ST elevation were carried out, as this patient was given digoxin treatment. Owing to pacemaker treatment, patient No. 36 was only subjected to 9 measurements of the ST elevation.

In order to evaluate the inter-individual variation, the hourly measurements of the ST elevation were related to time following the onset of symptoms. Table III shows that, with anterior AMI, 6 patients had a significantly positive correlation between ST elevation and time, whereas the correlation was significantly negative in 5 patients. From table IV it can be seen that with inferior AMI, 3 and 7 patients had positive and negative correlation, respectively between ST elevation and time.

Tables III and IV show the measured ST elevations related to the simultaneously measured heart rate. With anterior AMI, 5 patients had a significantly positive correlation between ST elevation and heart rate—in addition, these patients ST elevation was positively correlated to time. The 14 patients, with anterior AMI had significantly higher heart rate than the 15 control patients, on average 91 and 68 respectively ($p<0.001$). There was no difference in the heart rate of the 5 patients with significantly positive correlation between ST elevation and heart rate and the other 9 patients. In patients with inferior AMI there were 3 patients with a significantly positive correlation between ST elevation and heart rate, but there was no correlation in the remaining patients. Heart rate in patients with inferior AMI did not differ significantly from the heart rate of the control patients nor was there any difference in the heart rate of the 3 patients with positive correlation to the ST elevation and the remaining 13 patients.

method using several measuring series PSD= pooled standard deviation. k=the number of samples, df_i and SD_i^2 are the degrees of freedom (n_i—1) and the variance in sample i. PSD on double determinations was calculated according to the formula $PSD^2 = \frac{1}{2k} \sum_{1}^{k} d^2$ where d=the difference between 2 double determinations. The comparison of several correlation coefficients (r) was effected by means of the test statistic $\sum_{1}^{k} (n-3) \quad (z_i - \bar{z})^2$ as the distribution of the sample correlation coefficients can be normalized approximately by means of Fisher's z transformation $z = \frac{1}{2} \ln \frac{1+r}{1-r}$ and $r = \frac{e^{2z}-1}{e^{2z}+1}$ significance limit for X^2 distribution (3) Otherwise t test and F-test were employed. A significance level of 0 05 was chosen.

Results

Reliability of ST deviation measurement

The measurement of a set length by means of the digitizer gave an SD=0 06 mm With a change in the position of the paper between each measurement, the SD was 0 09 mm

The inter and intra-observer variation in the measurement of the ST deviation constituted a PSD of 0 16 mm and 0 18 mm respectively The measurement of the ST deviation with different electrocardiographs, produced a PSD of 0 15 mm

Table I shows the influence that the position of the patient had on the ST deviations when these were registered via a precordial lead Between the normal supine position and a left or right oblique position, the PSD was 0.24 mm and 0.21 mm respectively A F test showed that the measured PSDs of the variation in positioning of the patients did not differ significantly from the measuring error

The pooled variance and PSD of the measured ST deviations, taken every hour

Table I The influence of posture on the ST segment in a precordial lead.

Case no	ST deviation (mm) Left oblique position	Supine position	Right oblique position
21	4 0	3 9	3 4
	4 9	4.5	3 9
22	3 0	4 0	4 0
	4 0	4.2	4.3
23	1 8	1 9	2.1
	1 3	0.7	0 1
24	0.3	0.1	0 4
	0 6	0 9	0.7
25	1 9	2 0	2.0
	1 9	2.2	2.2
27	0.3	0 4	0.5
	0 4	0 4	0 4
28	0 4	0 4	0.1
	0 8	0.6	0 1
29	3 8	3 8	3 9
	3 9	3 4	3 6
30	3.2	3 1	3 0
	3.5	3 1	3.3
3?	1.7	1 9	1.7
	1 8	1 6	1 9
PSD	0.24 mm		0.21 mm

were 0 067 and 0.26 mm, respectively after recording via a precordial lead in 15 control patients, and 0 031 and 0 18 mm using aVF in 10 control patients. A F test showed that PSD=0.26 mm in the first control group was *significantly greater* than the PSD of 0 18 mm ($p<0.05$) for the measuring error but not significantly different from the PSDs of 0.24 mm and 0 21 mm for the variation in the position of the patient. A PSD=0 18 mm in the other control group corresponds to the PSD of the measuring error

Patients with AMI

Table II shows the numbers of the 14 patients who suffered from anterior AMI The capital letter followed by a figure indicates the position of the electrode to which the

ble IV Correlation between ST elevation and time ter onset f symptom heart ate mean arterial blood pre ure heart rate x systolic blood pressure and respiratory ate in patients suffering from inferior AMI

Case no.	Time r	n	P	Heart rate r	n	P	Mean arterial B.P r	n	P	Heart rate x systolic B.P r	n	P	Respiratory rate r	n	P
	—0.807	51	<0.001	0.236	51	n.s.	0.521	50	<0.001	0.468	50	<0.001	—0.373	49	<0.01
6	—0.023	41	n.s.	0.250	41	n.s.	0.225	38	n.s.	0.495	38	n.s.	0.173	39	n.s.
9	0.088	26	n.s.	0.063	26	n.s.	0.304	26	n.s.	0.316	6	n.s.	0.144	23	n.s.
10	—0.42	6	n.s.	—0.113	6	n.s.	0.424	5	n.s.	0.314	6	n.s.	0.318	4	n.s.
34	—0.720	5	<0.001	0.244	52	n.s.	0.234	48	n.s.	0.486	48	<0.001	—0.269	47	n.s.
36	0.695	9	<0.05	0.873	9	<0.01	0.910	6	<0.05	0.934	8	<0.001	—0.809	6	n.s.
41	0.364	49	<0.05	0.076	49	n.s.	—0.210	47	n.s.	—0.036	47	n.s.	0.005	47	n.s.
42	—0.196	29	n.s.	0.040	29	n.s.	0.410	27	<0.05	0.277	27	n.s.	—0.211	26	n.s.
43	—0.736	33	<0.001	0.331	33	n.s.	0.810	31	<0.001	0.659	33	<0.001	0.191	33	n.s.
46	0.113	51	n.s.	0.197	51	n.s.	—0.144	49	n.s.	0.166	49	n.s.	0.043	49	n.s.
47	—0.882	55	<0.001	—0.157	55	n.s.	0.477	55	<0.001	—0.061	55	n.s.	—0.242	55	n.s.
49	—0.353	54	<0.01	0.640	54	<0.001	0.71	50	<0.001	0.857	50	<0.001	0.118	50	n.s.
51	—0.418	53	<0.01	—0.118	53	n.s.	—0.005	51	n.s.	—0.069	51	n.s.	—0.164	49	n.s.
55	—0.087	49	n.s.	0.069	49	.s.	—0.017	48	n.s.	0.072	48	n.s.	0.157	48	n.s.
56	—0.575	44	<0.001	—0.263	44	n.s.	0.693	43	<0.001	0.681	43	<0.001	—0.572	43	<0.001
58	0.339	50	<0.05	0.402	50	<0.01	—0.181	49	n.s.	0.242	49	n.s.	—0.070	49	n.s.
X^2 distribution of ri df=15	194.084 P<0.0005			50.284 P<0.0005			99.685 P<0.0005			96.775 P<0.0005			35.364 p<0.005		

Table III *Correlation between ST elevation and time after onset of symptoms, heart rate, mean arterial blood pressure, heart rate x systolic blood pressure and respiratory rate in patients suffering from anterior AMI*

Case	Time			Heart rate			Mean arterial B.P			Heart rate x systolic B.P			Respiratory rate		
no	r	n	P	r	n	P	r	n	P	r	n	P	r	n	P
3	—0.642	8	n.s.	—0.453	8	n.s.	—0.491	8	n.s.	—0.492	8	n.s	—0.550	7	n.s
5	0.710	48	<0.001	0.760	48	<0.001	—0.137	47	n.s.	0.475	47	<0.001	0.614	47	<0.001
7	0.768	50	<0.001	0.800	50	<0.001	—0.243	50	n.s.	0.635	50	<0.001	—0.218	49	n.s
8	—0.992	5	<0.001	—0.392	5	n.s.	0.954	4	<0.05	0.991	4	<0.01	—0.518	4	n.s.
11	0.702	48	<0.001	0.578	48	<0.001	—0.315	48	<0.05	0.219	48	n.s.	0.415	46	<0.01
12	—0.330	13	n.s.	0.426	13	n.s.	0.569	13	<0.05	0.491	13	n.s	0.400	13	n.s.
14	—0.376	51	<0.01	0.008	51	n.s.	—0.080	48	n.s.	0.135	48	n.s	—0.017	48	n.s.
21	—0.462	49	<0.001	0.030	49	n.s	0.344	46	<0.05	0.404	46	<0.01	0.302	45	<0.05
22	0.625	51	<0.001	—0.277	51	<0.05	—0.321	47	<0.05	—0.387	47	<0.01	—0.035	47	n.s.
23	—0.627	57	<0.001	—0.045	57	n.s.	0.527	50	<0.001	0.444	50	<0.001	0.219	46	n.s
29	0.81?	48	<0.001	0.701	48	<0.001	—0.003	44	n.s.	0.524	44	<0.001	0.711	39	<0.001
31	0.709	50	<0.001	0.861	50	<0.001	—0.016	49	n.s	0.549	49	<0.001	0.332	48	<0.05
33	—0.673	36	<0.001	—0.084	36	n.s.	—0.341	33	n.s.	—0.550	36	<0.001	0.056	36	n.s
37	—0.260	50	n.s.	0.014	50	n.s.	—0.306	39	n.s.	0.044	39	n.s.	—0.138	38	n.s
X^2 distribution of r df=13	303.408 P<0.0005			156.593 P<0.0005			50.584 P<0.0005			84.998 P<0.0005			53.680 P<0.0005		

e II Correlation between ST elevation and time after onset of symptom heart rate mean arterial blood pressure heart rate x systolic blood pressure and respiratory rate in patient suffering from inferior AMI

Case No.	Time			Heart rate			Mean arterial B.P			Heart rate x systolic B.P			Respiratory rate		
	r	n	p	r	n	p	r	n	p	r	n	p	r	n	p
2	−0.807	51	<0.001	0.236	51	n.s.	0.521	50	<0.001	0.468	50	<0.001	−0.373	49	<0.01
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51	−0.418	53	<0.01	−0.118	53	n.s.	−0.005	51	n.s.	−0.069	51	n.s.	−0.164	49	n.s.
55	−0.087	49	n.s.	0.069	49	n.s.	−0.017	48	n.s.	0.072	48	n.s.	0.157	48	n.s.
56	−0.575	44	<0.001	−0.263	44	n.s.	0.693	43	<0.001	0.681	43	<0.001	−0.572	43	<0.001
58	0.339	50	<0.05	0.402	50	<0.01	−0.181	49	n.s.	0.242	49	n.s.	−0.070	49	n.s.
X^2 distribution of r df=15	194.084 P<0.0005			50.284 P<0.0005			99.685 P<0.0005			96.775 P<0.0005			35.564 p<0.005		

The ST elevation is also related to mean arterial blood pressure in Tables III and IV With *anterior AMI* there was positive correlation between these variables in 4 patients and negative correlation in 2 patients. With *inferior AMI* there was positive correlation between these variables in 7 patients, but correlation was absent in 9 patients

Tables III and IV show the relation between ST elevation and the product of heart rate and systolic blood pressure With anterior AMI 7 patients had a positive correlation between these variables and 4 patients also had a positive correlation between ST elevation and heart rate the remaining 3 patients had a positive correlation between ST elevation and mean arterial blood pressure. With inferior AMI 6 patients had a positive correlation between ST elevation and heart rate multiplied by systolic blood pressure of these, 5 and 2 patients also had a positive correlation between ST elevation and mean arterial blood pressure, and ST elevation and heart rate respectively

Tables III and IV also show the relation between ST elevation and respiratory rate. With anterior AMI there was a positive correlation between these variables in 5 patients whereas in the patients with inferior AMI there was no correlation, apart from 2 patients with negative correlation.

Tables III and IV also show the X^2 distribution of the correlation coefficients following z transformation In each group the X^2 is far greater than the chosen confidence limits as an expression of a very large dispersion of the correlation coefficients within the individual groups.

The presence of retrosternal pain or chest discomfort was registered based on information supplied by the patients. Comparisons were made with the paired t test between the measured ST elevation in patients with anterior AMI partly before and after the pain caused. In neither case was it possible to demonstrate that the pain had any influence on ST elevation

Patients with anterior AMI were studied for the influence of nasal oxygen therapy on ST elevation A comparison between the measured ST elevations before and after the administration of oxygen, and before and after the cessation of oxygen therapy respectively showed that oxygen treatment had no influence on ST elevation.

Discussion

In the present study the ST segment elevation during the early phase of AMI was followed in a single unipolar lead in anterior infarctions, the precordial lead giving the highest initial ST elevation was used, whereas in patients with inferior AMI the aVF lead was employed.

Our data of the reliability of the method showed that the variations of ST segment deviations in the control groups were of the same magnitude as the measuring error When the aVF lead was used the variation corresponded to the measuring error whereas use of a precordial lead produced a significantly greater variation of the ST deviations than that corresponding to the measuring error but the variations were not significantly greater than the total measuring error of the method, which included patient positioning

The investigation showed that the spontaneous course of hourly measurements of ST elevations for 48 hours after the onset of the infarction is marked by a pronounced variability This applied both to anterior and inferior infarction The intraindividual variation of the ST elevations in patients with AMI was significantly greater than in the control patients. The inter individual variation of the ST elevation in patients with AMI was also statistically significant The explanation which immediately suggests itself is that this pronounced variability of the ST elevations can be due to a corresponding variability in the clinical parameters as these influence or could have some connection with, the myocardial ischaemia, for instance oxygen treatment, retrosternal pain heart rate blood pressure or respiratory rate

Arterial hypoxaemia is common during the first few days after AMI (2) and it has

been demonstrated experimentally that hy potaemia increases ischaemic injury after coronary occlusion (12) It ha also been found that enrichment of inspired oxygen content reduced ST elevation as recorded in precordial mapping in human AMI (7) In our investigation, nasal oxygen therapy had no influence on ST elevation in patients with anterior AMI but t is possible that the administration of an oxygen flow of 2—6 l/min is too low to influence myocardial ischaemia.

Precordial ST *segment mapping* technique has shown that attacks of cardiac pain result in an increased ST elev tion (9) However in the present study the commencement and cessation of etrosternal pain or chest discomfort had no influence on the hourly measured ST elevations in patients with anterior AMI, although we had the impression that the information on chest discomfort obtained from the patients was imprecise in several cases. I this connection, the patient's pain threshold is of considerable importance.

The fact that increased heart rate also increases ischaemic damage has been demonstrated in experimental studies (8 13) A similar observation ha been reported in pa tients (14) In our investigation, a significant positiv correlation could only be demonstrated between ST elevation and heart rate in fewer patients, but this was perhaps due to the heart rate mainly falling within nor mal limits, where changes in myocardial ygen consumption are possibly too small to cause significant alteration in the ST segment.

The reduction in arterial blood pressur decreases myocardial wall tension and lowers myocardial oxygen requirements. If there is concomitant severe decrease in coronary perfusion pressure, there tendency for the myocardial oxygen del very to the ischaemic areas to be diminished also, and therefore to interfere with the beneficial effect on ischaemia obtained from the decrease in myocardial oxygen requirement (8 13) These two contrary effects of lowering arterial blood pressure can possibly be the cause of the investigation not demonstrating any pattern of the correlation coefficients between ST elevation and mean arterial blood pressure.

The product of heart rate and systolic blood pressure has been employed clinically as a reasonable indirect measure of the oxygen consumption of the myocardium (6) In patients with AMI a rising product should thus result in a rising ST elevation. In the present study significant positive correlation could be demonstrated between ST elevation and heart rate multipl ed by systolic blood pressure in almost one half of the patients.

When pulmonary disease can be exclu'ed in patients with AMI increased respiratory rate indicates the presence of cardiac insuff ciency which is usually related to the extent of the injured myocardium (2, 10) In the present investigation, 93 % of the patients had heart failure despite this, only 36 % of the patients with anterior AMI had positive correlation between respiratory rate and ST elev tion; in patients with inferior AMI there was no positive *correlation* between these variables.

Our results thus suggest that, in part, there was significant dispersion of the correlation coefficients within the individual groups in which a correlation was made between ST levation and heart rate, mean arterial blood pressure, heart rate multiplied by systolic blood pressure, and respiratory rate, respectively and partly that the correlation coefficients were variable between the d ffe rent groups. Thus the variability of the ST elevations wa most often inexplicable and only rarely attributable to alterations in the clinical status There can be several causes of this inconstant correlation. On the one hand, it is possible that the linical variables are poorly correlated to myocardial ischaemia when these variables mainly lie within nor mal ranges; this is in contrast to experimental conditions where the heart rate and blood pressure are artifically provoked to extreme values (8 13) with a subsequently greater influence on myocardial oxygen consumption. On the other hand, factors other than ischaemia might affect the ST segment, i.e. change in pH and ion concentrations, tempe rature changes, or sympathetic stimulation of

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Arterial hypoxaemia is common during the first few days after AMI (2) and it has

Rapid monitoring of regional myocardial ischæmia with echocardiography and ST segment shifts in man

Modification of "infarct size" and hemodynamics by dopamine and beta blockade

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Abstract

A multiaxis echocardiographic technique was applied to visualize the mechanical performance of the ischaemic and noninfarcted myocardial segments in 42 patients with acute myocardial infarction. The echo technique was used together with 12 lead electrocardiogram and Swan-Ganz thermodilution to study the immediate effects of graded dopamine infusions and beta blocking drugs on both hemodynamics and infarct size. Twenty patients were studied using dopamine, 19 of them with subsequent 5 mg dose of practolol. 0.2 mg of pindolol alone was given to 22 patients.

The acute and significant alterations of the ST segment shifts induced by such pharmacological intervention were accompanied by directionally similar changes in the contractile function of the ischaemic myocardial segments ($p<0.01$). The best agreement was noted between the reduction in the ST segment shifts and the recovery of mechanical function in the ischaemic segments after beta blockade: the concordance was [illegible] % ($p<0.01$).

Dopamine improved hemodynamic function markedly without arrhythmias ($p<0.001$). In nonfailing hearts dopamine constantly increased signs of ischaemia, but in 5 of the 6 patients with serious pump failure, dopamine improved circulation without worsening the ST segment ($p<0.001$). This was probably due to concomitant reduction of the left ventricular diameter ($p<0.0005$) and thereby of wall stress. The small intravenous dose of 0.2 mg pindolol was hemodynamically safe in the 22 patients with uncomplicated infarction and with moderate left heart failure: left ventricular filling pressure and stroke volume did not change, nor did any ventricular dilatation take place. The ST segments were improved by 30 % ($p<0.0005$) and the contractile function of the ischaemic segments improved markedly ($p<0.0005$) by 25.6 % of the normal, in 15 minutes in an average of 15 hours from the onset of symptoms. Practolol, given subsequent to dopamine and later 25 hours from the onset, also reduced these signs of ischaemia significantly though somewhat less than pindolol.

the heart (1 4) Consequently it would be misleading to suppose that changes in ST elevation during AMI reflect changes in myocardial *ischaemia only*

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Tabl I Noninvasive Techniques to Evaluate Infarct Size in Man.

	Time needed
Myocardial enzyme release (CK)	Hours
Radionuclide imaging	Hours to days
ST segment elevation	Minutes
Segmental myocardial function (echo)	Seconds

mechanical dysfunction of the ischaemic myocardium (22, 48, 63 64) In contrast, the hemodynamic overall pump function remains rather insensitive since t represents team work by both the ischaemic ones and the compensating uninvolved zones (6, 53)

W decided to study functional signs of ischaemia as rapidly as they are shown by ST segment shifts, but mor directly One indicator that can be used in practice for this purpose, though t has not so far been utilized in man, is segmental wall contraction.

This report concentrates mainly on the feasibility of using echocardiography to document the performance of regional myocardial function in acute ischaemia, i.e. both its recovery by beneficial drug intervention as well as its behavior as raped indicator of events which increase ischaemia. These direct signs of ischaemia were compared with simultaneous ST segment alterations. Our combined technique of myocardial segment — ST segment mapping seems to be rewarding clinical tool for rapid directional studies of ischaemic injury

R lationship between ST gment shifts and ischaemia

Electrophysiologically ST segment alter tions closely reflect myocardial ischaemic injury Extensive investigations have generally established tha acute epicardial and intramural ST segment shifts provide valid, sensitive and reproducible method for assessing ischaemic injury after experimental coronary occlusion (40 63) though in the center of very large injury ST segment elevation may be minimized (4 20) Thus, ST segment elevation correlates directly with myocardial oxygen and carbon dioxide tension, anaerobic metabolism, myocardial enzyme depletion, and subsequent light and electron microscopic histology (63) Alterations in the extent of electrocardiographic ischaemic injury are related to changes induced in myocardial xygen demand and coronary blood flow (20 26, 48 63) Surface electrocardiographic ST segment changes at the precordium reflect epicardial electrophysiology extremely closely and consistently (48)

Another important factor is that alterations of reversible myocardial injury ar mirrored almost instantaneously in changes in ST segment elevation (48) This relationship and the finding that the ST segment maps are stable in the absence of further myocardial damage (6, 35 37 40 59 66) permits the use of ST segments as rapid marker of ischaemia for intervention studies in patients with acute myocardial infarction.

However the ST segment shift only directionally with certain reservations (4 20, 48) indicates the increase or relief of ischaemic injury Percentual deviations of the initial ST segments are not quantitatively related to the later final mass of the infarct (20, 48 63) A better prediction of the final infarct size vailable from electrocardiograms by tudying the subsequent development of QRS changes in those leads initially showing ST elevations (3 39)

Nonischaemic causes of ST segment changes in patients with myocardial infarction are common, including conduction defects pericarditis, electrolyte alterations, drugs and electrode placement (23 48, 63) These disturbances can be largely voided in the short-term intervention studies where the patients serve as their own controls Clearly ST segment analysis provides useful noninvasive clinical tool that can be used to detect acute change in the severity of ischaem c injury at least, over relatively short periods of time (48, 63 66) The method is rapid, easy to use and directionally accurate.

ST segments in the present study were recorded from the standard 12 leads. The

For rapid characterization of myocardial ischaemia and infarction, the mechanical segmental function of the left ventricle by echo, together with the ST segments, provides an informative clinical method

Wavefront progression of ischaemic cell death a therapeutic challenge

Acute myocardial infarction is not a sudden permanent loss of myocardium In autopsy studies of patients dying of acute myocardial infarction tissue damage has often been found to occur in a progressive and scattered manner (2 7 12) The vulnerability of the subendocardial zones to ischaemia has been convincingly demonstrated (32 45 67) this is where the wavefront of the progressive myocardial ischaemia is initiated. In fact, ischaemic myocardial zones of very considerable size (30—50 %) can be salvaged by various types of pharmacological intervention up to six hours following the experimental total coronary artery occlusion (38) Otherwise, many hemodynamic circumstances and types of pharmacological intervention greatly increase the ischaemic injury (22)

In human myocardial infarction, the development of the final infarct size is delayed even more. A stepwise course has been reported biochemically and electrocardiographically in the majority (60 to 80 %) of patients (22, 26 31 42 59) Considerable extensions of the ischaemic damage at the "twilight zones" surrounding the center of the infarct may take place even over a period of several days. Both the short term and late prognoses of the patients after infarction are well known to be determined fundamentally by the extent of the resulting left ventricular dysfunction. Therefore, the new concept of limiting the infarct size (5) is becoming an increasingly important approach in early treatment. At least an inadvertent increase of the evolving infarct induced by certain drugs should be avoided.

Hemodynamic subsets infarct size and medical therapy

The great variety of hemodynamic subsets noted in patients with acute myocardial infarction (8 17) provides one rational basis for the selection of a specific form of treatment. The aim of therapy today should not only be hemodynamic support, but also the protection of the jeopardized ischaemic segments, which are often large. Treatment of hypovolemic hypotension by fluid challenge, or hyperdynamic cardiac action by beta blockade are examples of such physiological principles of therapy However the same therapeutic intervention may sometimes produce the opposite effect on the infarct size, depending on the prevailing physiological circumstances. For example reports on vasodilators and infarct size (10) and on inotropic drugs and infarct size (33 34) are controversial Information on the immediate effect of therapeutic intervention should be available quickly and easily in order to permit appropriate modification of the treatment instituted.

Methods for evaluating infarct size

Methods for a convenient quantitative assessment of the final *infarct size* in man are so far lacking. The methods applied have mainly been creatine phosphokinase enzyme release, electrocardiographic ST segment and QRS mapping, and myocardial imaging by radioisotopes (22) (Table I) The echocardiographic scanning technique developed recently by us also seems to provide a suitable method of describing the site and size of asynergic wall motions in infarction (18 51) However in the acute stage of evolution of the infarction, the proper application of pharmacological intervention should be controlled very rapidly it is useless to be told after several hours have elapsed that unsuitable treatment was going on, while waiting for the results' Of the methods in common use, only the electrocardiographic ST segment shifts are rapid enough to provide a means of immediately recognizing the directional course of the ischaem c process (Table I)

Evaluating ischaemic dysfunction, on the other hand can be done directionally very quickly using electrophysiologic and metabolic methods, and by studying the regional

traction in a few seconds (26 68 69). This relationship has been repeatedly documented experimentally by segment length and wall thickness measurements (4 28 64 65 68 74) (Fig. 1). Mechanical alteration even precedes the appearance of the ischaemic ST segment shifts, and precedes even more the onset of measurable biochemical alterations (26, 27). The functional aberration of myocardial contractility is thus obviously one of the most sensitive markers of ischaemia. Recovery after short ischaemia may be noted more rapidly in mechanical function than in the ST segments, while after longer ischaemia mechanical dysfunction persists despite normalization of the ST segments (4 64 69 72). Thus dissociation of these two sensitive markers of acute ischaemia, mechanical and electrophysiological, is sometimes possible, depending on the nature and time course of the ischaemic injury.

Experimentally, abnormalities of the myocardial segmental wall motions are directly and very accurately visualized by ultrasound (28, 69). Recently local contraction abnormalities have also been described by echocardiography constantly in patients with myocardial infarction (11 18). However detection of the regional contraction kinetics in the entire human left ventricle naturally requires multiple beam directions. We have developed a multiaxis single-beam echocardiographic technique called echoventriculography that is suitable for reaching almost every segment of the left ventricle (18, 51). Performance of the noninfarcted myocardium, the center of the infarcted area and the twilight zone between can be displayed using noninvasively and serially this technique in gravely ill patients. The method described in the following, together with rapid ST segment shifts and hemodynamic measurements, was therefore used for comprehensive study of instantaneous directional effects of pharmacological intervention on the function of ischaemic myocardial segments and hemodynamics in man. Beta stimulation and beta blockade were selected as ... types of intervention with physiologically opposite cardiac effects.

A technical description of echoventriculography for the detection of regional wall motion abnormalities of the left ventricle in man

The echoventriculography technique is based on the single-beam studies used sequentially from multiple directions to assess the segmental myocardial function of practically the entire left ventricle. Regional function can thus be studied from the upper and lower halves of the septal, anterior, lateral and posteroinferior left ventricular segments (18, 51).

The anatomical orientation is performed in a standard way and using four principal echo beam directions (Fig. 2) (51). Orientation is begun by finding the point on the chest wall from which the motion of both the anterior and posterior mitral leaflets is seen simultaneously. This point is usually situated in the 4th intercostal space about 1—2 cm left of the margin of the sternum, but there may be individual variations. The beam then meets the easily recognizable aortic root when the probe is moved upwards along the sternum. The anterior junction of the right ventricle and the septum is found by moving the probe from the left sternal border in a lateral direction and thereby tracing the narrowing of the right ventricular cavity towards the left ventricular anterior wall. The apex is recognized by the opposite motion of the anterior and inferolateral left ventricular walls downwards from the mitral point. The apical region of the left ventricle has also been reported by others to become well visualized by the low sites of the probe (11). The characteristic echoes of the anterior and posterior papillary muscles and the anterior and posterior edges of the mitral valve are other useful landmarks during orientation to the anterior, posterior, septal and lateral horizontal sectors of the left ventricular circumference.

When the probe is moved from the mitral recording point to the left sternal margin, without changing its horizontal plane, and directed slightly inferiorly, the conventional position (position 1, Fig. 2) for the left ven-

precordial ST mapping systems are applicable only to anterior and anterolateral infarctions. The convenient 12 lead electrocardiogram allows study of the inferoposterior infarctions, too in the same way as in the vector ST segment approach (1) The 12 lead electrocardiogram has been shown recently to give a good picture of the ST segment shifts recorded by the extensive mappings, and it also predicts the final extent of infarct necrosis in man (3 15)

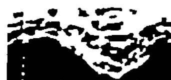
The sites of the precordial leads were modified somewhat to allow for the simultaneous precordial echocardiographic examination. The leads were permanently fixed and the recordings were always made with the patient in the same position. ST segment shifts were measured 60 msec after the termination of the QRS deflection and using the PR segment as the isoelectric line. If the ST segment was markedly depressed it was included in the sum of the ST segment elevation too since the ST segment depression occurring in these patients reflects either the subendocardial injury current or a reciprocal shift to the main ST segment elevation (see Fig 8)

Relationship between ischaemia and the mechanical performance of myocardium

Ischaemia of the myocardium is very closely related to the mechanical myocardial dysfunction. The ischaemic region loses its con-

WHY SEGMENTAL WALL MOTION DETECTS ISCHEMIA?

MYOCARDIAL CONTRACTION IS GREATLY REDUCED, OR LOST, IN ISCHEMIA


NORMAL WALL MOTION


ISCHEMIA 10 SEC


ISCHEMIA 30 SEC

ECHO EQUALS ANGIO IN SENSITIVITY FOR DETECTION OF REGIONAL ASYNERGY

Fig 1 The sequence of normal anterior wall segment motion changing into akinetic and paradoxical motion in increasing ischaemia is illustrated by echo in man. The time course is taken from the experimental coronary artery ligation (ref 68).

tricular transverse diameter is obtained. Left ventricular volumes and ejection fraction are usually calculated from these diameters using the cube function (14 51) The four standard precordial positions and axis directions are used for detailed assessment of the segmental wall motion (Fig 2) At each precordial position the probe is directed as perpendicularly as possibl towards the region desired. This is ascertained by rotating the probe with small steps and finding a direction so that the echo lines at the 2:1 scale from the myocardial layers move in a parallel w y in both the A-mod and M mode display (51 54)

The upper septal and posterolateral regions of the left ventricle are reached from position 1 (Fig. 2) Position 2 is about 2 cm lateral from the mitral val point, e. positions 1 and 2 are about 5 cm apart. Thus beam axis traverses the upper posterior and free anterior wall regions (Fig. 2) Position 3 of the probe lies one intercostal space below position 1 thus axis scans the inferolateral and septal regions in the lower half of the left ventricle. The low f ee anterior and inferoposterior wall regions ar recorded from position 4 one intercostal space below position 2 (Fig 2) These standardized scanning sites are necessary in order to obtain reproducible data in the sequential studies.

Additional positions are used for more detailed estimation of the anterior wall asynergy High anterior (AW5) septal-apical (AW6) and mid-anteroseptal (AW7) regions are scanned between the four standard sites at the anterior side f the lef ventricle (Fig. 2) Often even more lateral areas may be studied in cases where the left ventricle has enlarged laterally (AW8—14) (Fig. 2) The posterior wall segments are usually studied first. The same gain and reject levels are used for each segment. The fine adjustments are made by rotating the probe by slight movements according to the A-mode control. The regional M-mode scanning which ha repeatedly shown optimal endocardial and epicardial echolines is photographed with a Polaroid camera from the memory scope screen. The anterior wall regions are recorded in a similar way but a lower decibel gain is usually utilized.

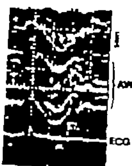
The regional myocardial function is analyzed quantitatively by measuring the amplitude of the systol c wall motions and the systolic thickening at each site. The velocity of systolic segment motions has not contributed anything to these measurements (49) The mean normal left ventricular anterior wall motion amplitude is 4 9—5 7±1 4 (s.d.) mm (AW1—4) and the mean normal posterior wall motion amplitude is 7 9—8.5±1.8 (s.d.) mm (PW1—4) (49) The difference is probably caused by the ecoil motion of the whol heart 1—2 mm anteriorly in systole (51)

The "total" regional function of the left ventricle is studied by summing up the individual regional wall motion amplitudes. The echoventriculographic contraction index (50) is obtained in this way from the sum of the ampl tude at the 8 standard sites (PW1—4 and AW1—4 Fig. 2) the sum is normalized by dividing it by the sum of the corresponding mean normal amplitudes (49 50) In left ventricle contracting asynergically this composite segmental function describes the teamwork of the normal, often hyper contractile, myocardium together with the asynergic segments (53)

While the echoventriculography technique markedly expands the capacity of the single beam echo to study the left ventricular performance in detail, t also poses many technical problems (51) Elderly emphysematous patients and obese subjects require considerably time and effort before acceptable recordings are obtained. Correct orientation to the particular segment in the repeated studies requires careful marking of the precordial sites used for the study thereafter t is easier to select the correct beam direction using the perpendicular echo line motion patterns.

Reliability f echoventriculogr phy in detecting the site and size f abnormal wall motion

The high accuracy of the multidirectional echoventriculography method in detecting

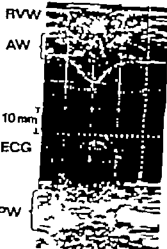


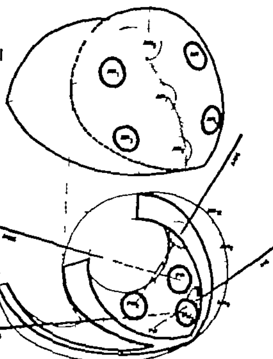
1 5 2 12 13 14
8 10
7
3 4 9 11
6











F g 2 The echoventriculogr phy t chnique s based on mult xis echobeam recording from various p ecord al sites The four basic preco dial transd cer site in the 4th and 5th inter costal spaces ar llustrated with respective schemati egments being scanned in the l ft ventricle The other precordial numbers refer to the add tional sites used fo study f the anterior wall Characteristic segment motion patterns seen n myocardial infarction in the 2 1 sc le ar also displayed The t ansverse xi pi t re f the left ventri le displays a parad xical moti n f the posterio wall

Table II Statistic of Differences in the Echocardiographic Dimensions Recorded in Patients with Acute Myocardial Infarction

	LV diastolic diameter		Healthy zone Amplitude		Wall thickness diastolic		Wall thickness systolic		Infarct zone Amplitude		Border zone Amplitude		Infarct+border zones Wall thickness diastolic		Infarct+border zones Wall thickness systolic	
Time interval (min)	0—10	0—60	0—10	0—60	0—10	0—60	0—10	0—60	0—10	0—60	0—10	0—60	0—10	0—60	0—10	0—60
S.E. (mm)	0.56	0.34	0.20	0.20	0.26	0.26	0.63	0.44	0.20	0.26	0.20	0.24	0.27	0.21	0.37	0.28
S.D. (mm)	1.37	0.90	0.49	0.54	0.63	0.63	1.53	1.07	0.45	0.70	0.49	0.65	0.89	0.78	1.[illegible]2	1.05
N	6	7	6	6	6	6	6	6	5	7	6	7	11	14	11	14

with chronic coronary artery obstruction verified by selective coronary arteriography. The wall motion of the ventricular segment known to be perfused by a markedly stenosed artery was measured 3 minutes after an increase in the heart rate with atrial pacing. Without a single exception the wall motion amplitude decreased during the pacing, and finally it often became paradoxical, in parallel with, but preceding, the appearance of the electrocardiographic ischaemic ST segment depression (Fig. 3). The left ventricular size also increased acutely instead of the normal reduction seen during pacing. Both the ischaemic myocardial segment motions and the ST segments normalized again within 2—3 minutes after the pacing was stopped. Besides confirming the sensitive physiological relationship between ischaemia and myocardial segmental function, this study also demonstrates the ability of the echoventriculography technique to document such changes rapidly.

Hemodynamic measurements

A Swan—Ganz thermodilution catheter No. 7 was advanced into the pulmonary artery branch and checked fluoroscopically. Cardiac output was determined as an average of 3 to 4 ice-cold saline injections measured with an Edwards 9510 thermodilution computer.

The pressure transducer zero was positioned at the mid-thoracic level. Arterial pressure was measured with a cuff sphygmomanometer with 2 mmHg reading interval. The following hemodynamic variables were recorded: heart rate, systolic and diastolic arterial pressures, pulmonary capillary wedge pressure, stroke volume, cardiac output, left ventricular stroke work and rate pressure product. The mean arterial pressure was approximated for the calculations by the sum of the diastolic pressure and one third of the pulse pressure.

Patients and study protocol

Forty-two patients, 36 men and 6 women, ranging in age from 34 to 78 (mean 55.2 years), were studied during the acute phase of what was usually their first unequivocal

regional ventricular asynergy has been proved by correlative studies with electrocardiogram, cineventriculography and autopsy findings in patients with myocardial infarction In acute myocardial infarction the presence of abnormal regional motion was confirmed in all subjects in a series of 30 consecutive patients (18) thereafter the same held true in about one hundred other patients. The septal anterior posteroinferior or lateral site of acute transmural myocardial infarction by serial electrocardiograms was in complete argeement with the location of the asynergic motion noted in echoventriculography

In 42 patients studied for coronary artery bypass surgery the left ventricular cineangiography was related to the echoventriculography (50) The presence of an asynergic segment in angiography was always correctly predicted by echoventriculography as was the quantitative degree of the abnormal motion Angiographically normal segments were similarly normal in echoventriculography(50)

So far 20 patients with fatal myocardial infarction were studied with echo shortly before death. The borders of the infarct were assessed by echo to fall into 7 equal sectors, each at the upper and the lower halves of the left ventricle At autopsy a variation over the sector determined echocardiographically was exceptional and only occurred at the furthest lateral wall and the posteroseptal areas, which are comparatively blind to the single beam (unpublished) Usually the borders of the infarct as shown by echo and a pathologic anatomic examination agreed within 1—2 cm

Reproducibility of echo measurements

The reproducibility of the present technique in *normal left ventricle* was tested in a series of healthy subjects (49) In 34 paired measurements the differences in the systolic wall motion amplitudes recorded 10 minutes apart remained insignificant the standard error of differences was 0 1 mm and the standard deviation of differences 0.7 mm. For the wall thickness in diastole these figures were 0.2 mm and 1.2 mm, respectively in systole 0 4 and 1.2 mm. Left ventricular end-diastolic diameters were studied in 39 paired comparisons. The standard error of differences was 0.3 mm and the standard deviation of differences 1.7 mm (NS) One month later the standard error of differences of all these variables in 53 paired studies also remained insignificant, the standard error of differences for the systolic wall motion amplitudes was 0 15 mm.

This reproducibility of the sequential measurements is highly dependent on the strict standardization of the probe directions relative to the anatomical reference sites described above. For the segmental wall motion the perpendicular beam direction must always be controlled by the parallel echo line motions from the different myocardial layers of the segment being examined

In acute myocardial infarction the echoventriculographic data were repeatedly studied in 7 patients in order to test the short term stability of abnormal segment function during the first day of infarction thereafter only slight changes are usually seen (52) The measurements were repeated first 5 to 10 minutes and then one hour after the initial examination. Here the precordial sites for the border zone segments were marked on the chest wall in the same manner as in the later intervention studies, to ascertain an identical orientation in the repeat studies. No significant variations were noted (Table II) The standard error of differences in the wall motion amplitudes and thicknesses at the healthy infarcted and border zone segments were each 0.2 mm and of the end-diastolic left ventricular diameter 0.7 mm. These reproducibility studies then confirm the value of studying the segmental function changes quantitatively in ischaemic hearts, too, as a framework for the intervention studies.

Pacing-induced myocardial ischaemia

We also demonstrated the sensitivity of myocardial mechanics as a marker of acute ischaemia by an atrial pacing of 5 patients

Table II Statistics of Differences in the Echocardiographic Dimensions Recorded in Patients with Acute Myocardial Infarction

	LV diastolic diameter		Healthy zone Amplitude		Wall thickness				Infarct zone Amplitude		Border zone Amplitude		Infarct+border zones Wall thickness			
					diastolic		systolic						diastolic		systolic	
Time interval (min)	0—10	0—60	0—10	0—60	0—10	0—60	0—10	0—60	0—10	0—60	0—10	0—60	0—10	0—60	0—10	0—60
S.E. (mm)	0.56	0.34	0.20	0.20	[illegible]	0.26	0.63	0.44	0.20	0.26	0.20	0.24	0.27	0.21	0.37	0.48
S.D (mm)	1.37	0.90	0.49	0.54	0.63	0.63	1.53	1.07	0.45	0.70	0.49	0.65	0.89	0.78	1.22	1.05
N	6		6	6	6	6	6	6	4	7	6	7	11	14	11	14

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Pacing-induced myocardial ischaemia

We also demonstrated the sensitivity of myocardial mechanics as a marker of acute ischaemia by an atrial pacing of 5 patients

segment elevations analyzed at 15 minute intervals in 20 patients were 10.6±7.8 and 11.4±10.1 mV (7.5 % difference). Heart rate variations analyzed in 13 patients were 83.1±31.3 and 80.1±31.5 (3.6 % difference) pulmonary capillary wedge pressures were 11.2±4.4 and 11.9±4.6 mmHg (6.3 % difference) and stroke volumes 71.7±29.7 and 73.7±28.6 (2.8 % difference). The echocardiographic variables for short-term stability without any intervention were reported earlier (T ble II). The w ll motion amplitude variations remained within 1 mm, as is the case in normal subjects (49).

Dopamine (Dopmin® Orion, Finland) infusion in 20 patients was first administered at rate of 250 µg per minute. After 5 minutes all the measurements were repeated. The time was kept short since catecholamines may rapidly increase myocardial ischaemia. If no deleterious effects were noted (chest pain, arrhythmias, marked elevation of ST segments, or increase i the heart rate by more than 30 beats per minute) the dopamine drip speed was ncreased to 500 µg/min (14 patients) in some cases thereafter to 750 µg/min. After these recordings were completed the infusion was stopped for half an hour.

Practolol The second control recording after 30 minutes of recovery was followed by an intra enous injection of 5 mg practolol (Eraldin ICI, England). The drug was injected over period of 2—3 minutes the same patients treated first with dopamine. The recordings wer made 15 minutes later. The effect of practolol was compared with the second batch of control data, recorded half an hour after dopamine w s stopped. Practolol was not given to 1 of these patients due to cardiogenic shock.

Pindolol After the control recordings, 0.2 mg pindolol (Visken Sandoz, Switzerland) was injected in 22 other patients, who were not studied using dopamine and practolol. The drug response was again studied 15 minutes later. All the statistical analyses were performed using the t-test for paired data.

Results

Dopamine

Hemodynamic performance increased significantly in all 20 patients with dopamine in a dose-dependent way (Table III). The average cardiac output increased by 21.6 % with the 250 µg/min dose and by 38.1 % with the 500—750 µg/min dose ($p<0.001$). The increase was due more to the stroke volume becoming ugmented (14.9 and 28.5 % $p<0.001$) than to the faster heart rate which increased by 7.5 % and 19.9 % with these respective dosages ($p<0.001$). The arterial pressure tended to rise with the larger dose only and so did the stroke work (13.1 to 21.1 %, $p<0.001$). The rate pressure product, reflecting the myocardial oxygen consumption (29) increased with increasing dose (5.6 to 13.4 % $p<0.001$). Pulmonary capillary wedge pressure decreased insignificantly by an average of 2 mmHg. Only one did dopamine induce frequent ventricular ectopic beats requiring that infusion be stopped n this patient the rate pressure product increased by one third.

Left ventricular regional performance Dopamine enhanced the motion amplitude of the healthy myocardium by 12.4 % (from 9.7±2.8 to 10.9±3.9 mm, $p<0.025$) but by no more with the larger dose (Table IV). The left ventricular end-diastol c diameter was markedly reduced from 51.7±6.2 to 48.0±±6.5 mm ($p<0.0005$). This 7.2 % decrease in diameter means a 20.0 % smaller end-diastolic volume by the cube function. However ro improvement occurred in the ischaemic myocardial segments (T ble IV Fig 4 and 5). The mean change after both doses f dopamine was only 0.1 mm. I 10 patients the combined segment function improved and in others t deteriorated. Similarly only a negligible increase (7.4 %, NS) was noted in the total" regional performance by the echoventriculographic contraction index, being the result of the enhanced motion of healthy myocardium and the ischaemic segments showing variable responses only.

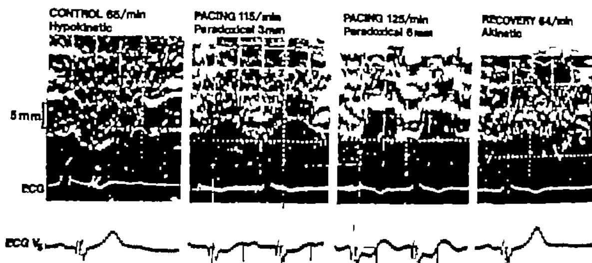


Fig 3 Myocardial ischaemia is induced with atrial pacing in a pat ent with coronary artery obstruction The initially hypok netic anteri r wall motion is changed drastically parad xical ST segment depression and anginal pain ppear ed simultaneously After stopping the pacing all changes were reversed

myocardial infarction. Five patients had a reinfarction, and 7 a nontransmural infarc tion The acute myocardial infarction was confirmed by chest pain, electrocardiogra phic serial changes and myocardial enzyme elevations. Twenty six patients had anterior and 16 posteroinferior infarction. Fourteen patients had uncomplicated infarction, 22 had clinically moderate heart failure and 6 had severe low output state cardiogenic shock or frank pulmonary edema (8) All patients were studied during the first 48 hours from the onset of pain the average time being 17 8 hours. About one half of the patients were studied between 12 and 24 hours after the onset of symptoms, 15 within 12 hours, and 5 after more than 24 hours. Informed consent for the procedure was obtained.

Twenty patients were studied using dopamine Of these 20 patients, 6 had uncom plicated infarction 8 moderate heart failure and 6 severe left ventricular failure Spe cifically we wanted to study any contrasting effects on signs of ischaemia induced sequen tially by both beta stimulation (dopamine) and beta blockade (practolol) in the same patients Nineteen patients were studied se quentially using dopamine influsions follow ed by practolol injection Twenty-two other patients received no inotropic stimulation, and the effect of beta blockade was studied using another beta blocking drug, pindolol

A period of 20—30 minutes was allowed for stabilization after application of the hemodynamic, electrocardiographic and echocardiographic recording systems The patients served as their own controls due to the short duration of the study In this way even the minor effects of intervention are better de fined despite the highly varied nature of acute infarction in individual patients. Eleven patients received lidocaine 1—2 mg/minute during the study Oxygen administration was kept unchanged throughout the study since this can influence the ST segments (36)

Control measurements were made repe atedly in each patient for hemodynamics and *ST segments* at 15 minute inter als to achieve a stable control state The variation in the repeated measurements remained non significant and virtually negligible The ST

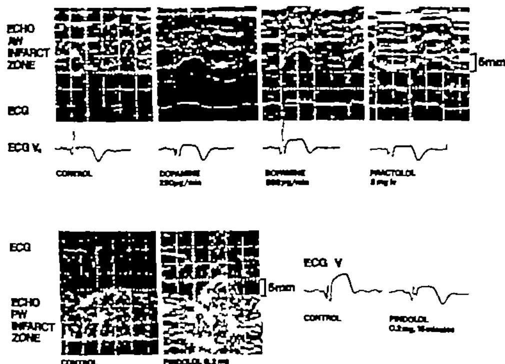


Fig 4 Illustrative wall motion changes f the ischaemic segment by echo Deterioration f the contractile function is progressive after increasing doses f d pamine Practolol thereafter di minished the paradoxical motion. A marked recovery f mechanical function is noted in another patient after pindolol. The ST segment changes are parallel

ST segments increased l ttle w th the small dose of dopamine (10.5 %, NS) but deteri orated markedly w th the larger dose (42 4 %, p<0.0025 Tabl IV Fig 6)

Dopamine and the hemodynamic subset of infarction. The acute effect of dopamine on the markers of ischaemia was influenced by the initial hemodynamic state of the patient. In 14 of the 20 patients who had uncom plicated infarction or moderate heart failure, dopamine alw ys made the ST segment de viations and the asynergic motion worse (Tabl V) In contrast, slight reduction of the ST segment by mean of —12.5 % (range —3 to —25 %) by the dopamine was noted in 5 of the 6 patients with severe left ventricular failure or shock after infarction in 2 of these this continued with the high dose as well (Fig. 7) The pulmonary capil lary wedge pressure decreased at the same time in 2 of the latter patients by mor than 5 mmHg, and improved mechanical function was also noted in their ischaemic segments.

Beta blockade by pindolol and practolol

Hemodynamic performance did not deterio ate n the 22 patients treated with a 0.2 mg dose of pindolol. These patients had an uncomplicated infarction or moderate left heart failure. The most significant change was the

Table III *Hemodynamic Effects of Dopamine Infusion in Patients with Acute Myocardial Infarction (Mean±SD)*

	Control	Dopamine 250 µg/min		Control	Dopamine 500—750 µg/m n	
	N = 20		P	N = 14		P
Heart rate (bpm)	83.7 ± 21.7	90 0 ± 23 4	< 0 001	86 8 ± 19.5	96 3 ± 21 1	< 0 001
Systolic blood pressure (mm Hg)	127 6 ± 17.5	126.0 ± 18 1	NS	129.5 ± 14 6	132 9 ± 19.5	NS
Pulmonary capillary wedge pressure (mm Hg)	12.7 ± 5 1	12.0 ± 5 0	NS	11 9 ± 5.5	10 8 ± 4 6	NS
Cardiac output (l/min)	6.0 ± 1 6	7.3 ± 1.7	< 0 001	6.3 ± 1.7	8.7 ± 2 4	< 0 001
Stroke volume (ml)	75 4 ± 25.8	86 6 ± 29.2	< 0 05	76 9 ± 29.2	98 8 ± 37.2	< 0 001
Stroke work (g m)	85 7 ± 27 6	96 9 ± 32 6		86 6 ± 30 0	104 9 ± 37 1	< 0 001
Rate pressure product (mm Hg bpm)	10634 ± 3286	11232 ± 3532	NS	10968 ± 2900	12438 ± 3102	< 0 01

Table IV *Myocardial Regional Function and ST Segment after Dopamine Infusion in Patients with Acute Myocardial Infarction (Mean ± SD).*

	Control	Dopamine 250 µg/min		Control	Dopamine 500—750 µg/min	
	N = 20		P	N = 14		P
LV diastolic diameter (mm)	51.7 ± 6.2	48 4 ± 6 9	< 0 0005	52.8 ± 6 1	49 0 ± 6.3	< 0 0005
Infarct zone amplitude (mm)	—1.7 ± 1 4	—1 9 ± 1 7	NS	—1 8 ± 1 4	—1 8 ± 2.3	NS
Border zone amplitude (mm)	2.7 ± 2.3	2.9 ± 3 4	NS	3.2 ± 1.7	4 0 ± 4 4	NS
Combined ischaemic zones amplitude (mm)	0 4 ± 2 9	0 5 ± 3 6	NS	0 9 ± 1 6	0 8 ± 4 4	NS
Healthy zone amplitude (mm)	9.7 ± 2 8	10 9 ± 3 9	< 0 025	9 4 ± 3.3	10 6 ± 3.7	NS
Echoventriculographic contraction index (%)	58.3 ± 20 1	62 7 ± 19.7	NS	62 3 ± 23 6	66.1 ± 18.7	NS
ST segment (%)	100	+10.5 ± 29.2	NS	100	+42.4 ± 49 6	< 0 0025

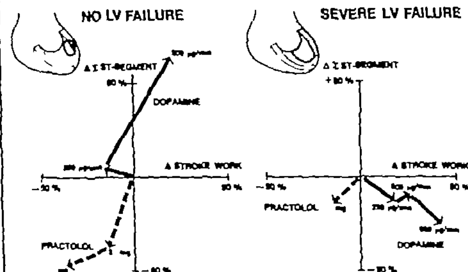


Fig 7 1 ... patient with uncomplicated acute myocardial infarction dopamine constantly increased ischaemic ST segment elevation while in severe pump failure marked hemodynamic improvement was often achieved without any electrocardiographic increase of ischaemia. A small dose of beta blocking drug intravenously effectively reduced signs of myocardial ischaemia it was often tolerable even in marked heart failure

Table VI Hemodynamic Effects of Pindolol in Patients with Acute Myocardial Infarction (Mean ± SD).

	Control	Pindolol 0.2 mg iv	P
	N = 22		
Heart rate (bpm)	75.4 ± 12.4	68.6 ± 9.7	< 0.001
Systolic blood pressure (mm Hg)	135.9 ± 23.6	128.8 ± 24.3	< 0.005
Pulmonary capillary wedge pressure (mm Hg)	13.2 ± 4.4	13.[illegible] ± 4.1	NS
Cardiac output (l/min)	5.6 ± 1.0	4.8 ± 1.3	< 0.01
Stroke volume (ml)	77.3 ± 17.6	72.1 ± 21.7	NS
Stroke work (g m)	94.8 ± 30.0	85.7 ± 32.7	< 0.05
Rate pressure product (mm Hg bpm)	10158 ± 2571	8831 ± 2089	< 0.0005

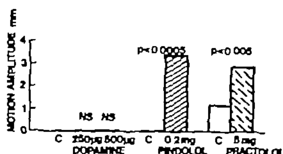


Fig 5 The mean change from control (C) in the systolic wall motion amplitudes of the ischaemic myocardial segments by echo remained zero after dopamine In contrast a remarkable recovery of the mechanical function was observed after small doses of beta blocking drugs

slowing of the heart rate by an average of 7 beats per minute (—9 0 % p < 0 001 Table VI) Cardiac output decreased by 14.3 % (p<0 01) due to the constant reduction of the heart rate while the stroke volume re mained virtually unchanged (—6 7 % NS) The left ventricular filling pressure remain ed very stable i.e. 13.2±4 4 mmHg before, and 13.2±4 1 mmHg after pindolol Left ventricular stroke work (—9 6 %) systolic arterial pressure (—5.2 %) and the rate pressure product (—13 8 %) all decreased significantly (Table VI) In one patient only pindolol caused a fall of arterial pressure by more than 20 mmHg

A rather exceptional demonstration of an obvious recovery of the ischaemic segments was the reduction of marked ischaemic papil lary muscle dysfunction in 2 patients imme diately after injection of pindolol (Fig 8)

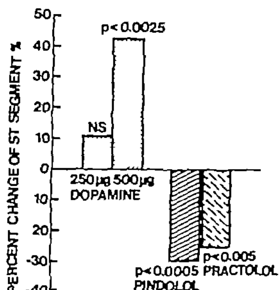


Fig 6 The sensitivity of the mean ST segment shift response to drugs increasing or decreasing cardiac work is displayed Practolol was given subsequently to the same patients who were first studied by dopamine

Left ventricular regional performance of the ischaemic heart was markedly modified by the small-dose beta blockade. The systolic motion both at the center of infarction and at the ischaemic border zone increased markedly by 0.2 mg of pindolol alone and somewhat less with 5 mg of practolol given subsequent to dopamine. With pindolol the improvement of the motions of both ischae mic segments analyzed together (infarct center +border zone) was from 0 1±3.5 to 3 4± ±3 6 mm (p<0 0005 table VII Fig 5) Re lated to the respective normal anterior and

Table V Hemodynamic Subset, Dopamine and ST Segment Shift

Subset	ST ↓	ST ↓>↑	ST ↑	Total
Uncomplicated or moderate left ventricular failure	0	6	8	14
Severe pump failure	5	0	1	6
				p < 0.001

Table VII Myocardial Regional Function and ST Segments after Pindolol in Patients with Acute Myocardial Infarction (Mean ± SD)

	Control	Pindolol 0.2 mg iv	P
	N = 22		
LV diastolic diameter (mm)	49.4 ± 6.2	49.5 ± 5.9	NS
Infarct zone amplitude (mm)	−1.1 ± 1.8	0.3 ± 1.9	< 0.0005
Border zone amplitude (mm)	1.2 ± 2.6	3.5 ± 2.5	< 0.0005
Combined ischaemic zones amplitude (mm)	0.1 ± 3.5	3.4 ± 3.6	< 0.0005
Healthy zone amplitude (mm)	9.3 ± 2.4	9.2 ± 2.6	NS
Echoventriculographic contraction index (%)	64.1 ± 17.1	75.6 ± 19.7	< 0.0005
ST segment (%)	100	−30.0 ± 20.9	< 0.0005

tinued to contract in a similar way before and after beta blockade the average amplitude decreased by only 0.1 mm with pindolol and 0.2 mm with practolol. Thus the "total" regional function assessed by an echoventriculographic contraction index improved by about 20 %, due to recovery of motion in the ischaemic segments. Neither did beta blockade cause any dilation of the left ventricular cavity size (Table VII and VIII).

ST segments improved by 30.0 % after pindolol (p<0.0005) and by 25.3 % after practolol (p<0.005 Tables VII and VIII Fig. 6). A minor deterioration (<10 %) of ST segments occurred in 1 of the 22 patients with pindolol and in 1 of the 19 patients with practolol.

Chest pain present in 13 patients during injection of the beta blocking drugs disappeared within 1—3 minutes in all these patients.

Table VIII Myocardial Regional Function and ST Segments after Practolol in Patients with Acute Myocardial Infarction (Mean ± SD).

	Control	Practolol 5 mg iv	P
	N = 19		
LV diastolic diameter (mm)	52.8 ± 6.3	51.8 ± 6.5	NS
Infarct zone amplitude (mm)	−1.6 ± 1.7	−0.5 ± 2.4	< 0.005
Border zone amplitude (mm)	2.9 ± 2.2	3.9 ± [illegible]3	< 0.025
Combined ischaemic zones amplitude (mm)	1.2 ± 2.4	2.9 ± 3.0	< 0.005
Healthy zone amplitude (mm)	9.2 + 3.0	9.0 ± 2.5	NS
Echoventriculographic contraction index (%)	55.0 ± 19.8	66.4 ± 27.3	< 0.025
ST segment (%)	100	−25.3 ± 30.3	< 0.005

posterior segment amplitudes (49) the fractional improvement is then 25 6 % after pindolol This change occurred without exception. The greatest improvement was a 9 mm increase in the motion of the ischaemic segments In 4 nontransmural infarctions, the mean improvement with pindolol by 5.5 mm exceeds the average value.

With practolol, the recovery at the ischaemic segments was from the control value of 1.2 ± 2.4 to 2.9 ± 3 0 mm after the drug, i.e. fractionally 13 1 % of the normal amplitudes (p<0 005 Table VIII Fig 5) The best improvement with practolol was a 7 mm increase in the ischaemic segments. A slight deterioration of less than 1 mm occurred in the ischaemic segments in 3 of the 17 patients (17.5 %) with practolol, and never with pindolol

Uninvolved myocardial segments conti

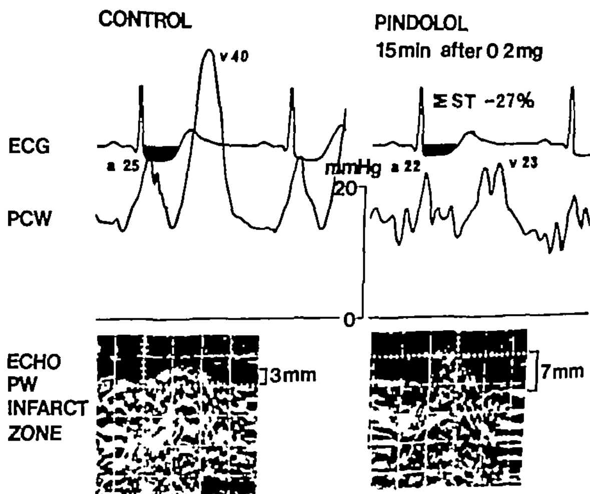


Fig 8 Marked ischaemic papillary muscle dysfunction in a patient with acute myocardial infarction produced a peak of 40 mmHg in the pulmonary capillary wedge pressure (PCW). After 0 2 mg pindolol intravenously the waveform of the wedge pressure is almost normalized Simultaneously ST segment depression (lead V6) indicating subendocardial ischaemic injury is reduced and the myocardial wall motion of the posterolated segment improved by echo from 3 mm to 7 mm The recovery of function in ischaemic myocardial segments explains the relief of the functional subvalve mitral incompetence

Table VII Myocardial Regional Function and ST Segments after Pindolol in Patients with Acute Myocardial Infarction (Mean ± SD)

	Control	Pindolol 0.2 mg iv	P
	N = 22		
LV diastolic diameter (mm)	49.4 ± 6.2	49.5 ± 5.9	NS
Infarct zone amplitude (mm)	−1.1 ± 1.8	0.3 ± 1.9	< 0.0005
Border zone amplitude (mm)	1.2 ± 2.6	3.5 ± 2.5	< 0.0005
Combined ischaemic zones amplitude (mm)	0.1 ± 3.5	3.4 ± 3.6	< 0.0005
Healthy zone amplitude (mm)	9.3 ± 2.4	9.2 ± 2.6	NS
Echoventriculographic contraction index (%)	64.1 ± 17.1	75.6 ± 19.7	< 0.0005
ST segment (%)	100	−30.0 ± 20.9	< 0.0005

nued to contract in similar way before and after beta blockade the average amplitude decreased by only 0.1 mm with pindolol and 0.2 mm with practolol. Thus the "total regional function assessed by an echoventriculographic contraction index improved by about 20 %, due to recovery of motion in the ischaemic segments. Neither did beta blockade cause any dilation of the left ventricular cavity size (Table VII and VIII)

ST segments improved by 30.0 % after pindolol ($p<0.0005$) and by 25.3 % after practolol ($p<0.005$ Tables VII and VIII Fig 6) A minor deterioration (<10 %) of ST segments occurred in 1 of the 22 patients with pindolol and in 1 of the 19 patients with practolol.

Chest pain present in 13 patients during injection of the beta blocking drugs disappeared within 1—3 minutes in all these patients.

Table VIII Myocardial Regional Function and ST Segments after Practolol in Patients with Acute Myocardial Infarction (Mean ± SD)

	Control	Practolol 5 mg	P
	N = 19		
LV diastolic diameter (mm)	52.8 ± 6.3	51.8 ± 6.5	NS
Infarct zone amplitude (mm)	−1.6 ± 1.7	−0.5 ± 2.4	< 0.005
Border zone amplitude (mm)	2.9 ± 2.2	3.9 ± 2.3	< 0.025
Combined ischaemic zones amplitude (mm)	1.2 ± 2.4	2.9 ± 3.0	< 0.005
Healthy zone amplitude (mm)	9.2 ± 3.0	9.0 ± 2.5	NS
Echoventriculographic contraction index (%)	55.0 ± 19.8	66.4 ± 27.3	< 0.025
ST segment (%)	100	−25.3 ± 3.03	< 0.005

posterior segment amplitudes (49) the fractional improvement is then 25 6 % after pindolol This change occurred without exception The greatest improvement was a 9 mm increase in the motion of the ischaemic segments. In 4 nontransmural infarctions, the mean improvement with pindolol by 5.5 mm exceeds the average value.

With practolol the recovery at the ischaemic segments was from the control value of 1.2 ± 2 4 to 2.9 ± 3 0 mm after the drug, i.e. *fractionally 13 1 % of the normal amplitudes* (p<0 005 Table VIII Fig 5) The best improvement with practolol was a 7 mm increase in the ischaemic segments. A slight deterioration of less than 1 mm occurred in the ischaemic segments in 3 of the 17 patients (17.5 %) with practolol and never with pindolol

Uninvolved myocardial segments conti

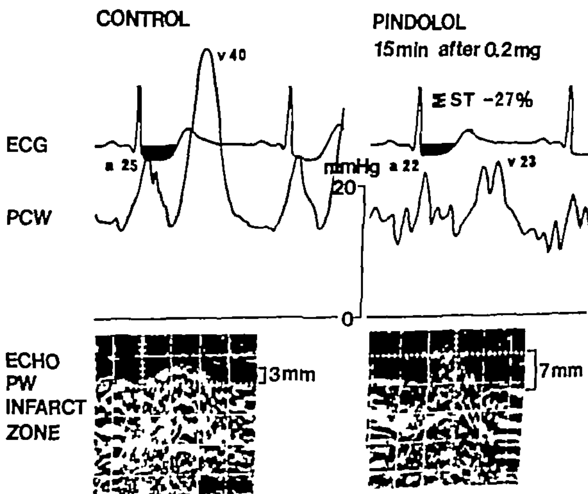


Fig 8 Mark d is haemic papillary muscle dysfunction in a patient w th cut myocardial infarction produced peak f 40 mmHg in the pulmonary c p llary wedge pressure (PCW). After 0.2 mg pindolol intravenously the wave f rm f the wedge pressure is almost n rmaliz ed S multaneously ST segment depressio (lead V6), ind ting subendocardial ischaemic jury is reduced and the myocardial wall motion f the posterolated segment s improved by echo from 3 mm to 7 mm The recovery of function in ischaemic myocardial segment explain the relief of the functional subvalvar mit al competence

function of the ischaemic myocardial segments is most consistent after beta blockade: the concordant course took place in 88 % of instances. Follow-up studies of our patients several days later indicated that this recovery remained permanent in most of them, too. Thus the possibility that the acute reduction in the ST segment elevation resulted from progression of the ischaemic injury to necrosis (4, 20) instead of from an improvement in its degree, does not sound plausible in view of the simultaneous and significant (p<0.0005) recovery of the contractile function at the ischaemic myocardial zones after beta blockade. The same holds true, though less strictly, with the directionally opposite changes after dopamine.

Particularly with minor ST segment deviations, or in nontransmural lesions with T wave changes only, the sensitivity of the myocardial segment motion by echo clearly surpassed that of the electrocardiographic analysis in documenting the acute directional changes taking place at the ischaemic zones. Whether reduction of acute transmural ST elevations of a marked degree will be quantitatively and not only directionally correlated with simultaneous recovery of the myocardial segment function, remains to be clarified.

Hemodynamic subset determining the selection of drug therapy

Dopamine effectively enhanced the cardiac pump function without excessive tachycardia or ventricular arrhythmia in patients with acute myocardial infarction, as reported by others (16, 24, 25). However, when used inappropriately in patients with moderate left heart failure only — not to mention uncomplicated infarctions — all inotropic drugs may rapidly and markedly increase ischaemic damage (22, 40). Both the ST segments and myocardial muscle mechanics acutely deteriorated, though initially even the ischaemic segments were responsive to the squeezing with inotropic demand, which has been demonstrated experimentally, too (26, 68). However, before long, with increasing ischaemia, this initial contractile improvement tended to deteriorate once more, like experimentally (68). This unfavourable course can easily be avoided during drug therapy by observing the steadily increasing ST segments. In clinical practice this danger is most prevalent in patients who are hypotensive due to hypovolemia (8, 16, 17). This kind of occasional divergent course of the ST segments and myocardial mechanics also emphasizes the usefulness of combining the segmental motion and ST segments for monitoring the fate of myocardial ischaemia.

Any inotropic treatment has been condemned now and then in acute myocardial infarction. This straightforward opinion was not confirmed in the present study with dopamine. These data indicate that the initial hemodynamic state, i.e. failing or nonfailing of the left ventricle, modifies the effect of the dopamine infusion on the ischaemic zones. The same contrast is evident experimentally: in uncomplicated myocardial infarction inotropic drugs increase the infarct size in dogs, while in depressed ventricles the inotropic improvement of the pump function is possible without any increase in ischaemic injury (40, 71). Such data have been lacking with human myocardial infarction. We found that when inotropic support was direly needed, a moderate dose of dopamine augmented the critically low pump function of the patients, without killing the jeopardized ischaemic segments either electrocardiographically or mechanically (Fig. 6 and 9). Here the reduction of the wall stress by the markedly reduced size of the dilated left ventricle (p<0.0005) after dopamine would overcome the opposite effects of the heart rate and contractility on the myocardial oxygen consumption (40, 71). Acute dilatation of the left ventricle is common in myocardial infarction (52, 61).

Compared with isoproterenol, dopamine did not adversely affect the ST shifts in experimental myocardial infarction, perhaps due to favourable effects on regional coronary blood flow (43) and myocardial metabolism (73), while in another experimental setting the findings remained variable (34). The vasodilating properties of dopamine in small

Correlation between mechanical function of ischaemic myocardial segments and electrocardiographic ST segments after drug intervention

The rapid changes of the contractile function in the ischaemic myocardial segments induced pharmacologically were compared directionally with the improvement or deterioration of the simultaneous electrocardiographic ST segment shifts. A discordant course was noted in only 18.8 %, or in 31 of 165 comparisons ($p<0.01$ sign test). With beta blockade alone, mechanical and electrical dissociation remained smaller 12.1 % (14 of 116 instanses after multiple doses $p<0.01$) than after the inotropic stimulation with dopamine where a divergent course was rather common 23.5 % (8 of 34 instances). This is reasonable, since under inotropic demand even the ischaemic myocardium is often mechanically responsible (26 58 68) but unfortunately often at the expense of rapidly increasing ischaemia and later deterioration. For ethical reasons this stimulation was not continued in most patients except transiently in 4 of the 14 patients treated with both doses of dopamine this sequence of the initial *improvement, contrasting with the deteriorating* ST segments, was thereafter found to become replaced by mechanical deterioration. One of the two variables remained unchanged in 31 of the 195 comparisons. Thus complete agreement directionally was noted in 69 % and partial agreement in 85 % of all the comparisons ($p<0.01$ for both)

In 8 of 41 patients beta blockade induced a marked improvement of contractile function while the usually initially minor ST segment shift, mainly in nontransmural infarction remained less than 10% Quantitatively no correlation was noted between the percentual reduction of the ST segments and the amount of improvement in the wall motion by beta blockade. Neither were ST segment shifts correlated quantitatively with changes in rate pressure product after beta blockade or dopamine although directionally the two variables were in excellent agreement

Discussion

Detection of the fate of ischaemic myocardial segments without delay

Since the myocardial infarction in general is larger in patients with pump failure and with serious ventricular arrhythmia than in those without them (2 7 27) any therapy to limit the amount of cardiac muscle killed during evolving infarction would seem to be extremely desirable. However measuring infarct size noninvasively in patients continues to be a problem. During application of the therapeutic intervention in particular at least a directional indication of the course of regional ischaemia should be known very rapidly. Otherwise, little hope remains for protecting ischaemic zones in an individual patient if the result is available only after several hours. This is the case, for instance, after attempts with enzymatic or myocardial imaging quantifications for ischaemia (22). The experience gained with the combined use of electrocardiographic ST segment mapping and the echoventriculographic myocardial segmental mapping" developed by us suggests the feasibility of using this technique for such studies. The method also seems to be quite accurate and very rapid.

Validation of the ST segment shift as an indicator of ischaemic injury

The degree of ST segment elevation in animals predicts the amount of later myocardial necrosis (13 63) although opinions differ somewhat (4 20). In man, there has been no direct evidence so far with other more specific methods that intervention reducing ST segment elevations really reflects a reversal of the ongoing ischaemic injury of the myocardium. Our data now indicate that the acute alterations of the ST segment shifts induced by pharmacological intervention are accompanied by directionally similar changes in the contractile function of the ischaemic myocardial segments. This applies to both the short term further elevation of the ST segments, and their significant reduction. The concordant reduction of the ST segment elevation with the recovery of contractile

Completely akinetic ischaemic segments were sometimes noted to recover almost normal contractility. This recruitment of the ischaemic segments (p<0.0005) clearly explains the preservation of adequate pump performance noted after beta blockade during the early stages of acute myocardial infarction. With the equivalent doses of 5 mg of practolol and 0.2 mg of pindolol, the latter seemed to reduce the signs of ischaemia more consistently and significantly. However the patient groups studied using practolol included more with pump failure, and most important, they had a longer duration of symptoms: an average of 23 hours in the practolol group and 15 hours in the pindolol group.

Interestingly enough, w ha e noted in preliminary studies that quite small doses of the beta blocking drugs used here produced most of the eduction noted in the signs of ischaemia. Increasing these doses of practolol and pindolol five-fold improved the ST segments or regional myocardial function only slightly but instead sometimes caused excessive bradycardia or trioventricular block. This very small dosage is in clear contrast to the rather massive beta blockade usually used in animal experiments to reduce infarct size (13 60).

The ability to reduce acute myocardial ischaemia is greater during the first few hours of infarction. However is note worthy that the various signs of ischaemia were highly significantly reduced by beta blockade much later too as this series included patients studied up to 48 hours from the onset of symptoms. This finding concurs with the concept of progressive, stutter ing course of acute myocardial infarction in man (2 7 12, 22, 26, 31 42, 59 66). Also, there is time to effectively protect ischaemic zones by therapy at least during the first tw days after the onset of symptoms.

I oncl sion, dopamine used with good judgemen is sometimes ery beneficial to patient w th serious low output state omplic ting acute myocardial infarction. I contrast, the inappropri te use of dopamine invariably increases ischaemia in nonfailing hearts. Small intravenous doses of beta block ing drugs seem to bring about a marked, safe reduction in the clinical, electrocardiographic and myocardial mechanical signs of ischaemia. Evidence was detected using direct echo visualization that the acute ST seg ment shifts indeed indicate a similar direc tional course in the mechanical function of the ischaemic myocardium in man. These noninvasive assessments may then prove to be of great clinical value in the characterization of myocardial ischaemia and infarction.

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doses (24) help one further to avoid an in creased afterload, unfavourable to the failing left ventricle (62) *In this series the systemic* vascular resistance decreased by one fourth with dopamine. In clinical practice, use of moderate elevation of arterial pressure to increase a shock level coronary and peripheral circulation is often unavoidable (16 17 47 78) even with the modern use of vasodil ators (10 62) In fact, the combined use of dopamine and nitroprusside evokes the best hemodynamic response in severe pump failure (10 44) Sometimes vasodilatory nervous reflexes cause marked hypotension (16 17) easily corrected by a small dopamine support.

However the presence of pump failure as such *is not always enough to determine the* use of inotropic therapy The easy monitor ing of ST segment behavior is very helpful *here in avoiding* at least the unnecessary use of inotropic support. Excessive infusion rates, even in patients with severe pump failure could cause a later loss of stability in the ischaemic segments, obviously due to inordi nately increasing vasoconstriction, contrac tility and heart rate (25) In this connec tion, the initial increase in the motion am plitude in the *uninvolved* segments also tend ed to become steady with the higher doses Whether this indicates excessive metabolic demand or myocardial segments being per fused by stenosed coronary arterial branches (53) remains unanswered.

Beta blockade in acute myocardial infarc tion. The small intravenous doses of the beta blocking drugs practolol and pindolol were hemodynamically safe, not only in the pa tients with uncomplicated infarction but also in those with moderate left heart failure. Left ventricular filling pressure and stroke volume did not change significantly after pindolol nor did the left ventricular cavity size change at all after each of these beta blocking drugs.

We selected these b ta blocking drugs due to their *cardioselective* and/or intrinsic sym-pathetic activities Such properties have been shown to depress contractility of the left ventricle less *than* propranolol (9) and the peripheral vasoconstriction which is unfavour able to the failing left ventricle (10 62) also remains less marked than with propra-nolol (41)

The favourable effect of practolol and pindolol on the reduction of myocardial mechanical and electrocardiographic signs of acute ischaemia was quite marked and consis-tent. Chest pain frequently disappeared at the same time as found by others (70) Re duction of the cardiac work is probably an obvious mechanism (5 30 38 46) (Fig 9) while counteraction of the deleterious effects of increased catecholamine content at the ischaemic zones (21 57) and the better myo-cardial metabolism and perfusion may con-tribute to it as well (46 47) Experimentally *Theroux et al. observed the same* partial functional sparing of the marginal segments after propranolol (69)

Improvement of the *ST* segments was of the same order as reported by others with usually relatively larger doses of propranolol (15) pindolol (19) or practolol (55 56)

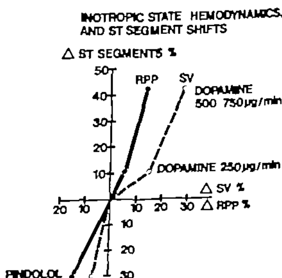


Fig 9 The mean increase decrease of the ST segment deviation by a beta stimulati g (dopamine) or beta blocking drug (pindolol) was re lated t chang of the rate pressure product which reflects myocardial oxygen consumption By the small dose f d pamine the strok volume (SV) was increased relatively more than the te pressure work with pindolol the de-crease f troke volume was insignificant

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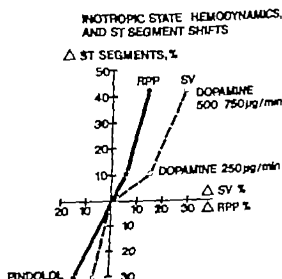


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Tabl 1 STI values and ischaemic ECG-variables in 24 male patients with previous myocardial infarction. Figures are mean ± 1 SD

Variable		All MI N= 4		Normal N=49	Ant. MI N=14		Inf MI N=8	One MI N=17	≥ 2 MI N=7	NYHA 1—2 N=17		NYHA 3—4 N=7
QS_2I	ms	511 ± 23		505 ± 16	507 ± 26		520 ± 18	509 ± 24	516 ± 19	518 ± 18	×	496 ± 28
LVETI	ms	375 ± 25	×	388 ± 12	369 ± 28		387 ± 15	374 ± 27	375 ± 18	385 ± 16	3×	350 ± 28
PEP	ms	116 ± 11	3×	94 ± 12	170 ± 9	×	110 ± 11	115 ± 12	119 ± 6	113 ± 11	×	123 ± 8
PEP/LVET × 10^3		448 ± 82	3×	345 ± 49	475 ± 90		406 ± 66	448 ± 93	451 ± 47	416 ± 62	2×	526 ± 77
S-ASAT	U I	228 ± 143		—	274 ± 149	×	140 ± 97	243 ± 159	195 ± 93	196 ± 146		291 ± 144
_R	mm	56 ± 27		—	49 ± 19	×	69 ± 34	50 ± 22	72 ± 28	60 ± 29		47 ± 17
_Q	mm	29 ± 20		—	37 ± 21	2×	14 ± 8	28 ± 19	33 ± [illegible]	28 ± 19		33 ± 22
_ST	mm	5.4 ± 3		—	6.4 ± 3		4.4 ± 3	5.7 ± 3	4.6 ± 3	4.4 ± 2	×	7.9 ± 4
Log $\frac{_R \times 10^3}{\Sigma Q \times _ST}$		2.67 ± 0.66		—	2.48 ± 0.67	×	3.07 ± 0.41	2.67 ± 0.66	2.69 ± 0.71	2.84 ± 0.68	×	2.21 ± 0.30

Level of significance: × = $p < 0.05$ 2× = $p < 0.01$ 3× = $p < 0.001$ See text for explanation of abbreviations.

Left ventricular function after myocardial infarction Relation between systolic time intervals and quantitative ischæmic ECG changes

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Abstract

Twentyfour male patients with sustained myocardial infarction (MI) were studied with 12 lead ECG and systolic time intervals (STI) 5 months after the acute episode. From the ECGs were calculated the summed voltages of the R wave (ΣR) the Q wave (ΣQ) *and the ST segment deviation (ΣST)* These ischaemic ECG variables were correlated with the STI parameters of left ventricular function LVETI PEP and PEP/LVET Statistically significant regression equations relating the ECG changes to the STI variables were found in anterior MI for ΣST in the entire series, but not in inferior MI Thus a simple and rapid inspection of the resting 12 lead ECG gives an indirect but reliable quantitative estimate of left ventricular function in patients with a sustained myocardial infarction.

Experimental studies have shown a relation between QRS changes in the ECG and the size of myocardial infarction (MI) (11 21) As the extent of myocardial damage after MI determines the impairment of left ventricular (LV) function (14 20 25) a correlation between QRS changes and the LV performance would be expected Linear correlation between the summed R wave voltages (ΣR) and the number of Q waves (Q index) and the angiographically determined LV ejection fraction has been reported in patients with chronic ischaemic heart disease (2, 4) This study looked for a quantitative correlation between the LV performance as reflected by various systolic time intervals (STI) and ischaemic ECG changes (ΣR, ΣQ and ΣST) in a group of patients with previous MI

Material and methods

The patients were 24 men aged 45—71 years (mean 57,5) with a definite MI in their history *The time from the last MI to the* ECG and STI recording was in median 5 months, range *1—17 months. Fourteen* patients had anterior MI 8 had inferior MI and 2 had both. Seventeen had one MI and 7 had 2—3 MIs. According to the N.Y.H.A. classification of heart diseases, 17 were in class 1—2, and 7 were in class 3—4

The patients were studied on their usual medication but with beta-blocker therapy withheld for at least 2 days. A conventional ECG (12 leads) and the STI variables were recorded. The patients were resting supine and Elema Schönander phonomicrophone EMT 25B with amplifier EMT 22 was used for the carotid tracing, a transducer EMT 510C (time constant 4 sec) and the Mingograf 34 3-channel jet ink writer were employed.

The ECG lead II phonocardiogram and carotid pulse tracing were recorded simultaneously at a paper speed of 100 mm per second. The ECG calibration was carefully

Table III Anterior MI (N = 14) Regression equations correlating STI variables with ischaemic ECG changes

		r	p
LVETI	$= -4.820\ \Sigma ST + 398$	−0.61	< 0.05
PEP	$= 1.612\ \Sigma ST + 109$	0.62	< 0.05
PEP/LVET × 10^3	$= 17.615\ \Sigma ST + 363$	0.59	< 0.05
PEP	$= -0.266\ \Sigma R + 133$	−0.56	< 0.05
PEP/LVET × 10^3	$= -2.646\ \Sigma R + 605$	−0.56	< 0.05

STI variables vs. ΣQ and index. No significant correlation.

Table IV Patients with 1 MI (N = 17) Regression equations correlating STI variables with ischaemic ECG changes

			p
LVETI	$= -4.450\ \Sigma ST + 399$	−0.56	< 0.01
PEP	$= 1.612\ \Sigma ST + 106$	0.47	< 0.10
PEP/LVET × 10^3	$= 16.7\ \Sigma ST + 354$	0.61	< 0.01

STI variables v. ΣR and ΣQ. No significant correlation

Table V Patients with ≥ 2 MI (N = 7) Regression equations correlating STI variables with ischaemic change on ECG

		r	p
LVETI	$= 0.570\ \Sigma R + 334$	0.89	< 0.01
PEP/LVET × 10^3	$= -1.4\ \Sigma R + 548$	−0.81	< 0.05
PEP	$= 0.232\ \Sigma Q + 112$	0.80	< 0.05

STI variables ΣST. No significant correlation

adjusted to 10 mm deflection = 1 0 mV From the ECG baseline (=T—P segment) the deflections of the Q wave, the R wave and the maximum ST segment elevation or depression were measured to the nearest 0.5 mm in every lead and summed to give the ΣR ΣQ and the ΣST respectively in millimetres. The QS_2 and LVET intervals were measured to the nearest 5 milliseconds, and the PEP and PEP/LVET were calculated in the usual manner The heart rate was determined and used for the calculation of the corrected value LVETI This calculation used *correction factors* derived from STI measurements on 49 normal men studied in our laboratory As part of the acute diagnosis of *MI* the serum aspartate aminotransferase (S-ASAT) was *determined* and *its* peak value taken as an approximate marker of myocardial damage

Regression equations and correlation coefficients *(r)* were calculated and t tested using standard statistical methods.

Results

Table I shows the findings in and the differences between the various subgroups of patients. Except for the QS_2I the STI variables are clearly abnormal compared with the control group Between anterior MI and inferior MI significant differences are seen in PEP in S-ASAT and as could be expected in ΣR, and ΣQ No significant differences are seen between the patients with one MI and those with ≥ 2 MI s. Between the clinical markers of left ventricular dysfunction the NYHA class 1—2 and 3—4 significant differences in all the STI variables are seen. This difference is also reflected in ΣST and in the compound ECG-index (Log $\frac{\Sigma R \times 10^3}{\Sigma Q \times ST}$) Table II shows the correlation between left ventricular (LV) function, as assessed by the LVETI PEP PEP/LVET and the calculated ECG variables ΣR ΣST and the compound indices in all the MI patients. The ΣR and ΣQ show no significant correlation with the LV function, whereas the compound indices show a weak but significant correlation with PEP/LVET Table III IV and V show the same correlations in the various patient subgroups. In patients with one MI no significant correlation existed between peak S-ASAT values during the acute MI phase (= a possible *marker of infarct size) and LV function,* as judged by the STI variables, or by the ECG variables ΣR, ΣQ and ΣST (Table VI)

Table II All MI patients (N = 24) Regression equations correlating STI variables with ischaemic ECG changes

		r	p
LVETI	$= -3.267\ \Sigma ST + 392$	$-0\ 45$	$<0\ 05$
PEP	$= 1\ 406\ \Sigma ST + 109$	$0\ 45$	$<0\ 05$
$PEP/LVET \times 10^3$	$= 1.3\ \Sigma ST + 379$	0.54	$<0\ 01$
$PEP/LVET \times 10^3$	$= -17\ 6\ Index_1 + 495$	$-0\ 43$	$<0\ 05$
$PEP/LVET \times 10^3$	$= -59\ 0\ Index_2 + 607$	$-0\ 47$	<0.05
STI variables vs ΣR and ΣQ No significant correlation			

$$Index_1 = \frac{\Sigma R}{\Sigma Q + \Sigma ST} \qquad Index_2 = Log\ \frac{\Sigma R \times 10^3}{\Sigma Q \times \Sigma ST}$$

Table III Anterior MI (N = 14) Regression equations correlating STI variable with ischaemic ECG changes

		r	p
LVETI	= — 4.820 ΣST + 398	— 0.61	< 0.05
PEP	= 1.612 ΣST + 109	0.62	< 0.05
PEP/LVET × 10³	= 17.613 ΣST + 363	0.59	< 0.05
PEP	= — 0.266 ΣR + 133	— 0.56	< 0.05
PEP/LVET × 10³	= — 2.646 ΣR + 605	— 0.56	< 0.05
STI variables vs. ΣQ and index. No significant correlation.			

Table IV Patients with 1 MI (N = 17). Regression equations correlating STI variables with ischaemic ECG changes

		r	p
LVETI	= — 4.450 ΣST + 399	— 0.56	< 0.01
PEP	= 1.612 ΣST + 106	0.47	< 0.10
PEP/LVET × 10³	= 16.7 ΣST + 354	0.61	< 0.01
STI variables ΣR and ΣQ- N significant correlation			

Table V Patients with ≥ 2 MI (N = 7) Regression equations correlating STI variables with ischaemic changes in ECG

		2	p
LVETI	= 0.570 ΣR + 334	0.89	< 0.01
PEP/LVET × 10³	= — 1.4 ΣR + 548	— 0.81	< 0.05
PEP	= 0.232 ΣQ + 112	0.80	< 0.05
STI variables ΣST No significant correlation			

adjusted to 10 mm deflection = 1.0 mV. From the ECG baseline (=T—P segment) the deflections of the Q wave, the R wave, and the maximum ST segment elevation or depression were measured to the nearest 0.5 mm in every lead and summed to give the ΣR, ΣQ and the ΣST respectively in millimetres. The QS_2 and LVET intervals were measured to the nearest 5 milliseconds and the PEP and PEP/LVET were calculated in the usual manner. The heart rate was determined and used for the calculation of the corrected value LVETI. This calculation used correction factors derived from STI measurements on 49 normal men studied in our laboratory. As part of the acute diagnosis of MI, the serum aspartate aminotransferase (S-ASAT) was determined, and its peak value taken as an approximate marker of myocardial damage.

Regression equations and correlation coefficients (r) were calculated and t tested using standard statistical methods.

Results

Table I shows the findings in and the differences between the various subgroups of patients. Except for the QS_2I, the STI variables are clearly abnormal compared with the control group. Between anterior MI and inferior MI significant differences are seen in PEP, in S-ASAT and as could be expected, in ΣR, and ΣQ. No significant differences are seen between the patients with one MI and those with ≥ *2 MI s. Between* the clinical markers of left ventricular dysfunction, the NYHA class 1—2 and 3—*4 significant differences in all the STI* variables are seen. This difference is also reflected in ΣST and in the compound ECG-index (Log $\frac{\Sigma R \times 10^3}{\Sigma Q \times ST}$). Table II shows the correlation between left ventricular (LV) *function, as assessed by the LVETI, PEP, PEP/* LVET and the calculated ECG variables ΣR, ΣST and the compound indices in all the *MI patients. The ΣR and ΣQ show no* significant correlation with the LV function, whereas the compound indices show a weak, *but significant correlation with PEP/LVET.* Table III, IV and V show the same correlations in the various patient subgroups. In *patients with one MI, no significant correlation* existed between peak S-ASAT values during the acute MI phase (= a possible *marker of infarct size)* and LV function, as judged by the STI variables, or by the ECG variables ΣR, ΣQ and ΣST (Table VI).

Table II. All MI patients (N = 24). Regression equations correlating STI variables with ischaemic ECG changes

		r	P
LVETI	$= -3.267\ \Sigma ST + 392$	−0.45	<0.05
PEP	$= 1.406\ \Sigma ST + 109$	0.45	<0.05
PEP/LVET × 10³	$= 1.3\ \Sigma ST + 379$	0.54	<0.01
PEP/LVET × 10³	$= -17.6\ Index_1 + 495$	−0.43	<0.05
PEP/LVET × 10³	$= -59.0\ Index_2 + 607$	−0.47	<0.05
STI variables vs. ΣR and ΣQ: No significant correlation			

$Index_1 = \frac{\Sigma R}{\Sigma Q + \Sigma ST}$ $Index_2 = \text{Log}\ \frac{\Sigma R \times 10^3}{\Sigma Q \times \Sigma ST}$

Table III Anterior MI (N = 14) Regression equations correlating STI variables with ischaemic ECG changes

		r	p
LVETI	$= -4.820\ \Sigma ST + 398$	−0.61	< 0.05
PEP	$= 1.612\ \Sigma ST + 109$	0.62	< 0.05
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PEP	$= -0.266\ \Sigma R + 133$	−0.56	< 0.05
PEP/LVET $\times 10^3$	$= -2.646\ \Sigma R + 605$	−0.56	< 0.05

STI variables vs. ΣQ and index No significant correlation.

Table IV Patients with 1 MI (N = 17) Regression equations correlating STI variables with ischaemic ECG changes

		r	p
LVETI	$= -4.450\ \Sigma ST + 399$	−0.56	< 0.01
PEP	$= 1.612\ \Sigma ST + 106$	0.47	< 0.10
PEP/LVET $\times 10^3$	$= 16.7\ \Sigma ST + 354$	0.61	< 0.01

STI variables ΣR and ΣQ No significant correlation

Table V Patients with ≥ 2 MI (N = 7) Regression equations correlating STI variable with ischaemic change in ECG

		r	p
LVETI	$= 0.570\ \Sigma R + 334$	0.89	< 0.01
PEP/LVET $\times 10^3$	$= -1.4\ \Sigma R + 548$	−0.81	< 0.05
PEP	$= 0.232\ \Sigma Q + 112$	0.80	< 0.05

STI variables ΣST No significant correlation

Table VI Correlation matrix for peak S-ASAT values v STI and ECG variables in 17 patients with 1 MI

	r"	
LVETI	0 22	All are n. s.
PEP	— 0 32	
PEP/LVET	— 0.34	
ΣR	— 0.22	
ΣQ	— 0 18	
ΣST	0.35	

Of the 13 patients with ΣR > 55 mm, 31 % had PEP/LVET > 0 44 (= normal value ± 2SD) in contrast to the 11 patients with ΣR ≤ 55 mm of whom 72 % had a PEP/LVET ≥ 0 44 However this difference is not statistically significant.

Discussion

Ischaemic ECG changes in man have been related to coronary artery disease as judged by arteriography (10 17 26 27) to LV contractile patterns (the Q wave) (5 18) to myocardial metabolic derangement, and to myocardial blood flow (the ST segment) (12, 22 23) and more recently to LV function, as determined by the ejection fraction (the R wave and Q index) (2, 4)

The amount of necrotic myocardium after an acute myocardial infarction directly determines the degree of functional impairment of the left ventricle (14 20 25) If information contained in the standard 12 lead ECG is quantitatively or directionally related to parameters reliably estimating LV function, we then have a simple and noninvasive means for estimating the amount of myocardial damage and the size of an MI The work of some clinical investigators has made it probable that such LV functional information is present in the 12 lead ECG Askenazi et al (2) showed a weak but statistically significant correlation between the angiographically determined LV ejection fraction and the summed R wave voltage of 8 ECG leads. Other authors reported the number of Q waves in a precordial map to be correlated to the ejection fraction and the extent of LV segmental dyssynergy (4 18) As with the clinical usefulness of the ST segment changes in the ECG in the acute phase of MI as markers of acute myocardial ischaemia or infarct size, we should not expect a perfect linear correlation but directionally similar changes in the ECG markers of myocardial tissue damage and other pertinent variables, invasive or noninvasive, of LV function (6, 8)

Measurement of the systolic time intervals has been widely applied in chronic ischaemic heart disease and was reported by many workers to give a reliable quantitative estimate of the LV function when compared with invasive parameters (1 9 13 15 16, 24) From the work by Eddleman et al (7) it seems that elevated values of PEP/LVET exceeding 0 440 almost always denote decreased LV ejection fraction to be less than 50 %

In this study we found a weak but statistically significant correlation between the noninvasively determined LV function, as expressed by STI variables, and possible quantitative ECG markers of myocardial necrosis ΣR, ΣQ and ΣST We recognize that STI measurements describing LV function are very indirect and that the correlation with the ECG variables is still far from being a direct expression of LV function, but our findings support the use of ΣR and Q index as indicators of LV performance, as found by others (2 4) except that the ΣQ in our study was the poorest marker

The use in this study of compound ECG indices (see Table II) did not improve the correlation with the STI variables, but served as an indicator separating the NYHA class 1—2 from the class 3—4 patients, thus confirming a relation between quantitative ECG variables and clinical markers of the severity of myocardial damage.

The correlation between the ΣST ΣR, and the various STI variables in anterior MI indicates that, although not a perfect quantitative relation the standard ECG a clinically useful indicator of myocardial damage

In inferior MI, no correlation was found in this study But it is possible that the use of only the pertinent ECG leads II III and aVF for the ΣR and ΣQ calculation and a larger patient series might show results similar to those in the anterior MI group

Patients with 1 MI did not show any correlation between S-ASAT and ischaemic ECG changes or STI variables this agrees with the findings of Norris et al (19) that no relation exists in the acute MI phase between enzyme levels and ΣST changes or clinical or haemodynamic variables. However persisting ST segment elevations, as expressed by the ΣST in this study apparently correlate with LVETI and PEP/LVET (Table IV)

In the group of 7 patients with ≥ 2MI s, the correlation between, on one hand, the STI variables and, on the other ΣR and ΣQ was excellent, despite there not being any significant difference between the individual variables (STI or ECG) in this group and the group with 1 MI (Table V)

Although not significant, a ΣR < 55 mm is associated with PEP/LVET exceeding 0.44 and thus probably a LV ejection fraction < 50 % A similar relation was found by Askenazi et al (2)

The relation between the ECG ariables and LV function also suggests a possible role of ΣR and ΣQ as markers of possible results of various infarct-limiting interventions (3 11)

The immediate clinical implication of this study is that simple and rapid inspection of standard 12 lead ECG gives an indirect but reliable quantitative estimate of the LV function in patients with previous myocardial infarction.

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Table VI Correlation matrix for peak S ASAT values v STI and ECG variables in 17 patients with 1 MI

	r	
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ΣQ	— 0 18	
ΣST	0.35	

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In this study we found a weak but statistically significant correlation between the noninvasively determined LV function, as expressed by STI variables, and possible quantitative ECG markers of myocardial necrosis ΣR, ΣQ and ΣST We recognize that STI measurements describing LV function are very indirect and that the correlation with the ECG variables is still far from being a direct expression of LV function, but our findings support the use of ΣR and Q index as indicators of LV performance, as found by others (2 4) except that the ΣQ in our study was the poorest marker

The use in this study of compound ECG indices (see Table II) did not improve the correlation with the STI variables, but served as an *indicator* separating the NYHA class 1—2 from the class 3—4 patients, thus confirming a relation between quantitative ECG variables and clinical markers of the severity of myocardial damage

The correlation between the ΣST ΣR and the various STI variables in anterior MI indicates that, although not a perfect quantitative relation the standard ECG is a clinically useful indicator of myocardial damage

Rocket immunoelectrophoresis of myoglobin in urine in patients with myocardial infarction

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Abstract

A rocket immunoelectrophoretic method with prepared antisera to rabbit myoglobin has been developed to study the urinary myoglobin excretion in patients with acute myocardial infarction. The method is able to detect minimum urinary myoglobin concentration of 1—2 mg/l. Urine specimens from 156 patients admitted to the coronary care unit with a provisional diagnosis of acute myocardial infarction were analysed. Seventysix patients proved to ha e documented myocardial infarction Twelve of them had at least one positive determination Four of the 80 without infarction had myoglobinuria. 15 hours elapsed from the time of the initial event of chest pain to the first positive urine specimen. N statistically significant difference could be demonstrated in the mortality in patients with infarction with and without myoglobinuria.

The present authors were unable to confirm the high incidence of myoglobinuria in acute myocardial infarction, described previously in other works. The possibility of enal tubular reabsorption of myoglob as an explanation of this descrepancy is mentioned. Our preliminary results with the estimate of myoglobin in serum with a radioimmunoassay seem to valuable as an index of infarct size.

Acute myocardial infarction (AMI) is generally diagnosed on the basis of a cha recteristic clinical history and typical electrocardiographic and serum enzyme findings. In patients with recent chest pain, and an old infarct pattern, or bundle branch block, these data are insufficient to establish the diagnosis definitely Therefore efforts ha been made to find more sensitive and possibly more specific tests, which might aid in documenting the presence and extent of myocardial necrosis. Damage to the cardiac muscle mass results in release to the circula tion of myoglobin, a low molecular weight, oxygen binding heme protein, which is found in and syntesized by cardiac and skeletal muscle (4) Present methods fail to detect the presence of myoglobin in the circulation or the urine. Several investigators have reported tha some patients with AMI develop myoglobinemia and myoglobinuria (mgu) which have been detected immunologically (2, 4 14)

W have developed ocket immunoelectrophoretic method for detecting myoglobin in urine to evaluate the frequency of mgu in patients with AMI

Material and method

Patients

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Rocket immunoelectrophoresis of myoglobin in urine in patients with myocardial infarction

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Abstract

A rocket immunoelectrophoretic method with prepared antisera to rabbit myoglobin has been developed to study the urinary myoglobin excretion in patients with acute myocardial infarction. The method is able to detect a minimum urinary myoglobin concentration of 1—2 mg/l. Urine specimens from 156 patients admitted to the coronary care unit with a provisional diagnosis of acute myocardial infarction were analyzed. Seventysix patients proved to have documented myocardial infarction. Twelve of them had at least one positive determination. Four of the 80 without infarction had myoglobinuria. 15 hours elapsed from the time of the initial event of chest pain to the first positive urine specimen. No statistically significant difference could be demonstrated in the mortality in patients with infarction with and without myoglobinuria.

The present authors were unable to confirm the high incidence of myoglobinuria in acute myocardial infarction, described previously in other works. The possibility of renal tubular reabsorption of myoglobin as an explanation of this descrepancy is mentioned. Our preliminary results with the estimate of myoglobin in serum with radioimmunoassay seem to valuable as an index of infarct size.

Acute myocardial infarction (AMI) is generally diagnosed on the basis of characteristic clinical history and typical electrocardiographic and serum enzyme findings. In patients with recent chest pain, and an old infarct pattern, or bundle branch block, these data are insufficient to establish the diagnosis definitely. Therefore efforts have been made to find more sensitive and possibly more specific tests, which might aid in documenting the presence and extent of myocardial necrosis. Damage to the cardiac muscle mass results in release to the circulation of myoglobin, a low molecular weight, oxygen binding heme protein, which is found in and syntetized by cardiac and skeletal muscle (4). Present methods fail to detect the presence of myoglobin in the circulation or the urine. Several investigators have reported that some patients with AMI develop myoglobinemia and myoglobinuria (mgu) which have been detected immunologically (2, 6, 14).

We have developed a rocket immunoelectrophoretic method for detecting myoglobin in urine to evaluate the frequency of mgu in patients with AMI.

Material and method

Patients

We studied 156 consecutive patients with a diagnosis of possible AMI admitted to the coronary care unit during an 8-month period. Urine samples were collected from each patient in the first three days, beginning on day of admission. The average time for the onset of chest pain to admission was 16 hours.

Diagnostic criteria

A standard 9 lead electrocardiogram was performed daily on each patient for 3 consecutive days and analysed for definite myocardial infarction or no infarction according to the criteria of Kjøller (8) Venous blood was taken daily for the first 3 to 5 days for estimating serum glutamicoxaloacetic transaminase, serum lactic dyhydrogenase and serum creatine Seventysix patients were found to have definite AMI Eighty patients failed to fulfil the diagnostic criteria. They constituted the control group The mean age of the infarction group was 65 0 years (44—84) and of the control group 63.8 years (22—83)

Preparation of myoglobin

Myoglobin isolated from human skeletal muscles obtained at operation, was prepared according to Luginbuhl (11) and further purified by gelfiltration on columns of G-100 and G-25 Sephadex The purified myoglobin eluate was freezedried

Immunization of rabbits

Antisera to human heart myoglobin were kindly supplied by Bengt W Johansson, Heart section, General hospital, Malmö, Sweden.

Rocket immunoelectrophoretic procedure

Rocket immunoelectrophoresis a.m. Laurell (9) involved the following techniques 0 075 M barbital buffer (pH 8.6) was employed in the electrode vessels. To 100 ml of 0.1 M glycine-saline buffer (pH 8.2) was added 1 gm of agarose A 37 and 6 gm of poyethylene glycol 4000 Ten ml of this mixture and 300 µl antihuman myoglobin were added to the immunoplates (100—100 mm) Wells, each 2.5 mm in diameter were then punched into the agar With the purified myoglobin as a standard 3 µl of undiluted urine was added to the plates. The electrophoresis was continued for 2 hours with a stabilized current of 50—60 mA (140—200 V on the power supply) The plates were rinsed in saline 154 M for 2.5 minutes and dried for 30 minutes at about 25 C and finally in a thermostat at 60°C. The quantitation of myoglobin in the samples and in the standard solutions (2, 5 5 10 and 20 mg myoglobin/1) were based on comparison of the immunoprecipitates from the upper edge of the application well to the top of the peak. The sensitivity of the method is 1—2 mg myoglobin/1 urine. Addition of myoglobin concentrations from 2—20 mg/1 urine has shown recovery from 85—110 %

Urine samples analysed

Urine was collected for each six-hour period for 3 days, and potassium hydrogencarbonate (800 mg/100 ml urine) was instantly added (pH 8 0—8.5) to prevent destroying the myoglobin content. The urine samples were stored at — 20°C until study

Table I Number of patients with acute myocardial infarction related to the presence of myoglobinuria and to the time from the initial event of chest pain The mortality in patients with and without myoglobinuria is shown

Hours from acute event	No of patients with positive tests.	No of patients with negative tests.
0—6	3	15
6—12	2	28
12—24	4	13
> 24	3	8
	12	64
Mortality	4 (33 %)	8 (16 %)

Results

Twelve patients with AMI had mgu (16 %). The mortality was 33 % among infarct patients with mgu, and 16 % among patients without mgu, similar to the total material (Table I). These differences are statistically insignificant ($p > 0.05$). None of the patients with mgu had previous muscle trauma. DC was not undertaken. No correlation was found between the time from initial event of chest pain and the frequency of mgu (Table I). Most of the 80 patients without AMI suffered from ischaemic heart disease (IHD). 10 had chronic bronchitis, pulmonary embolism or pulmonary neoplasm (Table II). The test for myoglobin was positive in 4 of which 3 had IHD and 1 pulmonary neoplasm (Table II). In 10 patients with AMI serum-creatinine was raised (> 1.5 mg/100 ml). Five of them had mgu (mean se-creatinine 3.9). Mean se-creatinine was 2.4 mg/100 ml in the other 5 patients (Table III).

Table II. The final diagnose in 80 patients without myocardial infarction. Three patients had more than one diagnosis

Diagnoses	No.	No. with positive tests
Ischaemic heart disease	57	3
Myocarditis	1	
Exacerbation in chronic bronchitis	6	
Pneumonia	2	
Pulmonary embolism, pulmonary neoplasm	3	1
Duodenal ulcer (X-ray verified)	2	
Gallstones	2	
Other	10	

Table III. Serum-creatinine values in 10 patients with acute myocardial infarction and chronic renal failure related to the presence of myoglobinuria

	Serum-creatinine values (mg/100 ml)				
AMI + mgu	3,3	1,8	3,9	7,8	4,9
AMI — mgu	1,8	1,9	2,0	2,4	3,8

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Discussion

Myoglobinuria after myocardial infarction has been assayed by various immunological techniques. Adams and Elliott (1) tested urine by haemagglutination inhibition assay and found myoglobinuria in 34 of 44 patients with myocardial infarction, and in 16 without obvious cardiac muscle disease. Levine and co-workers (10) using the same tech nique found mgu in 34 of 37 patients after myocardial infarction Only 1 of 28 patients with other cardiopulmonary diagnosis had myoglobinuria. Saranchak and Bernstein (13) with radial immunodiffusion technique found mgu in 59 of 60 patients and none in the control group Kagen and co-workers (6) demonstrated mgu in 3 of 7 patients with AMI By means of a complementfixation test, the authors found no correlation between myoglobinemia or myoglobinuria. Kessler and co-workers (7) found myoglobinuria in 15 of 24 patients. None in the control group had mgu. Donald and co-workers (3) using a haemagglutination inhibition method, found that 14 of 16 patients with definite myocardial infarct had mgu. None of the 17 patients with possible infarct had mgu.

We found mgu in 12 of 76 patients with definite myocardial infarction (16 %) and in 4 of 80 patients without infarction.

Studies on the renal handling of low molecular weight proteins (especially lysozyme) (12) show that these are filtered freely through the glomerulus membrane. In the proximal tubular cells, these proteins are resorbed and released to the circulation either as intact molecules or as catabolic products. The occurrence of myoglobin in the urine therefore will depend on the amount of filtered myoglobin. The exact renal thres hold for myoglobin is obscure but based on animal experiments, a value of 10—20 mg/100 ml serum seems reasonable (5)

Studies in serum from AMI patients (14) show that the myoglobin concentration in serum seldom exceeds 1 mg/100 ml These findings reasonably explain the few positive results in our studies. In patients with disturbed tubular function, a loss of low molecular weight proteins via urine have been demonstrated. In accordance with this, 5 of 10 patients in the present study with raised se-creatinine and AMI had mgu.

We conclude that detection of myoglobinuria is ineffective as a diagnostic method for AMI probably due to a tubular resorption of myoglobin. However our preliminary results with estimates of myoglobin in serum seem to be valuable as an index of infarct size.

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PANEL DISCUSSION

Bengt W Johansson A diagnosis of acute myocardial infarction is often easy to verify *In many instances, however the common* diagnostic armamentarium is not enough and a clearcut diagnosis cannot be given. This is so especially in patients who on admission have ECG changes due to a previous infarction, bundle branch block or intraventricular conduction disturbances, and in patients with a long time interval between onset of symptoms and admission to hospital Furthermore *uncharacteristic symptoms or multiple* attacks of chest pain in many patients will make it impossible to decide precisely when the infarction started an enzyme peak might have occurred before admission to the hospital.

To obviate these difficulties, new aids to diagnose an acute myocardial infarction have been developed. Those most often discussed in living patients during recent years are ST *mapping*, specific cardiac isoenzymes, radionuclides, and myoglobin in urine or serum

The early statement that CK MB is a cardiospecific isoenzyme has been questioned, and recent reports have claimed that a certain percentage of CK MB is found in tissues other than cardiac, including skeletal muscle. This might be of importance in patients with an impaired peripheral circulation due to an acute infarction. As the amount of skeletal muscle is much greater than the amount *of cardiac muscle even a small* leakage of CK MB from skeletal muscle will influence the serum values. Moreover there are technical difficulties that, from a clinical point of view might be of minor importance.

Some pitfalls in the determination of S creatine kinase B-subunit activity with an immunoinhibition method

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We recently described an immunoinhibition method for routine determination of S-CK B subunit activity (1 2) This method is based *on the SCE recommended* S-CK method ± ± antibody (3) Completeness and specificity of the immunoinhibition were achieved by the earlier described titration experiments with anti M (1)

In contrast to existing commercially available, one step S-CK MB procedures, our method comprises correction *for individual* adenylate kinase (EC 2 7 4 3 AK) sample blank activities, correction for the very small residual fraction of non-inhibited CK MM activity and correlation of S-CK B results to total S-CK activity The method has for more than a year been in routine use on the LKB 8600 reaction rate analyzer in our laboratory

We make 3 separate measurements on each sample

1) S-CK B in the presence of anti M
2) Total S-CK
3) S-AK activity

Previous studies have shown that the immunoinhibition of CK *MM is 99 0—99.7* per cent complete. However with the AMI discrimination limit for S-CK B set at 15 U/l (2) even 1 per cent of a total S-CK activity of 1500 U/l in a non AMI patient would appear as a *false* positive S-CK B result. In order to avoid any contribution of *residual non inhibited* CK MM activity an arbitrary 1 per cent of the total S-CK acti

ROUTINE DETERMINATION OF CK B ACTIVITY IN SCE CK METHOD ANTI-M		
CK REAGENT	ENZYME ACTIVITIES MEASURED	CALCULATION
+ANTI-M	CK B <1% of CK MM AK	APPARENT CK B
−ANTI-M	TOTAL CK CK MM CK MB CK BB (AK)	1% of TOTAL CK
−ANTI-M −CREATINE PHOSPHATE	RESIDUAL AK Erythrocyte Thrombocyte Liver Muscle	AK
		CK B

Fig 1

vity was consequently subtracted from the directly measured S-CK B activity (Fig. 1)

One of the main problems in the deter mination of S-CK B activity is the inter ference by AK (4 5 6) AK activity in serum originates from several sources includ ing erythrocytes, thrombocytes, liver and muscle tissue (4 5 6) One of the innov tions in the SCE CK reagent was the com bination f tw AK inhibitors, AMP and P[1] P[5]-di adenosine 5-pentaphosphate. A de tailed description has been given of the efficiency and specificity of thi inhibitor combination (4 5 6)

It inhibits 99 % AK from erythrocytes and muscle and about 90 % from liver However residual AK activity is inev tabl and can to greater or lesser degree contri bute to f lsely increased, apparent S-CK B activity Table I shows cumulative fre quency distribution of 1367 AK sample blanks from AMI and non-AMI patients. As our routine procedure incorporates a determination of individual sample AK blank activity f ll correction for this interference

Table I Cumulative frequency distribution of 1367 S-AK blank ates measured in the SCE CK reagent without creatine phosphate

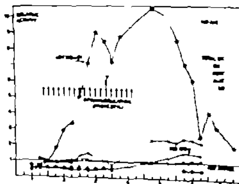
N	U/l	Per cent
509	0— 3.7	37.2
707	0— 7 4	88.9
102	0—11 1	96 4
29	0—14.8	98.5
20	>14.8	100.0

has been carried out in all S-CK B deter minations.

An evaluation of 288 non AMI patients showed that, with the used discrimination limit of 15 U/l (2) for S-CK B activity 56 false positives (19 per cent) were voided by this correction (T ble II)

Examples are given below that demon strate the specificity of the S-CK B deter minations achieved by the described correc tions.

The first example (Fig. 2) is where S-CK B activity constituted less than 0.5 per cent of a highly increased total S-CK activity A 73 year ld man was admitted to the CCU with suspected acute myocardial infarction. For one to two weeks before admission, he had suffered attacks of chest pain suggestive of angina pectoris. Serum enzyme determina



F g 2.

Table II Frequency of S AK values that would have caused false positive S-CK B results if S AK sample blanks had not been subtracted

	Number of patients	Samples
Non AMI patients, total	288	1055
Non AMI patients in which subtraction of individual S-AK (sample blanks)[1] reduced increased S-CK B values to <15 U/l	56 (19 4 %)	77 (7.3 %)

1 after subtraction of 1 % of total S-CK from apparent S-CK B

tions were made on admission and subsequently at six hour intervals.

The horizontal line at 1 on the ordinate represents the upper reference limit for each enzyme except for S-CK B where the line represents the discrimination value. (CK MB=0) and (LD iso) designate the time when isoenzyme electrophoreses were performed. The initial values of S-aspartate aminotransferase (S-ASAT) S-alanine aminotransferase (S-ALAT) total S-CK and S-CK B activities were within the reference range, whereas S-lactate dehydrogenase (S LD) was slightly above

After admission, the patient developed a ventricular arrhythmia. This was treated with intramuscular injections of procaine amide (Pronestyl®) at four hour intervals. Within eight hours after the first injection, total S-CK activity had increased by a factor of 4 It reached peak values of about 1500 U/l to 1700 U/l where it remained during the next four days.

The clinicians diagnosed the condition as non-myocardial infarction. This was supposed on the basis of the patient's history ECG lacking the criteria for AMI and on the routine enzyme analyses then available. The diagnosis agreed fully with the enzyme pattern plotted in Fig 2 In this case, S-CK B would have been well above the discrimination limit of 15 U/l unless subtraction of 1 per cent of total S-CK had been made

Fig. 3 shows the sensitivity of the immunoinhibition system. Both cases in this figure showed only relatively moderate elevations of total S-CK activities. The upper panel represents a 67 year old female who suffered intermittent chest pain attacks (arrows in figure) before the rise in serum enzyme activities. S-CK MB and S-LD H_4 isoenzymes were elevated electrophoretically in the samples indicated in the figure. Total S-CK and S-ASAT were increased, thus confirming the diagnosis of AMI (2) S-CK B activity was above the discrimination limit and showed a time course parallel with that of total S-CK. ECG was suggestive of an anterior wall infarction but was not conclusive The lower panel in Fig 3 represents a 59 year old female who had suffered chest pain

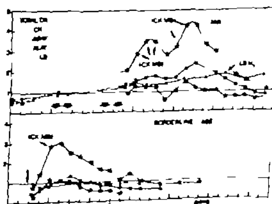


Fig 3

Table III Examples of non-AMI patients in which subtraction of 1% of total S-CK prevents false positive CK B values.

Patient age ♂ ♀	Clinical situation	Serum Enzymes (U/l) Total CK	Uncorrected CK B	AK	CK B — AK	CK B — AK — 1% of tot. CK
♂ 67	Biliary occlusion	72	22.8	16.8	6.0	5.4
♂ 45	Chest pain, non AMI	108	15.6	9.6	6.0	4.8
♂ 59	Ventr. fibr. non AMI	120	18.6	12.0	6.6	5.4
♂ 56	Myalgic pain	138	24.6	16.2	8.4	7.2
♀ 78	Heart failure	144	17.4	10.8	6.6	5.4
♂ 76	Heart failure	192	18.0	6.0	12.0	10.2
♂ 72	Angina pectoris	360	19.2	4.2	15.0	11.4
♀ 73	After orthop. surgery	540	21.0	5.4	15.6	10.2
♂ 63	Pulmonary embolism	660	19.2	3.0	16.2	9.6
♂ 39	Repeated I.M. inj.	936	25.8	4.2	21.6	12.0
♂ 25	After phys. excercise and possible viral myositis	984	18.6	3.0	15.6	6.0
♂ 56	After orthop. surgery	1320	22.2	3.0	19.2	6.0

Table IV

Predictability of S-CK B

	Neg	Pos	
AMI	1	52	53
non AMI	56	0	56
	57	52	Total 109

PV Pos = 1.0
PV Neg = 0.98

Predictability of total S-CK

	Neg	Pos.	
AMI	0	53	53
non AMI	51	5	56
	51	58	Total 109

PV Pos = 0.91
PV Neg = 1.0

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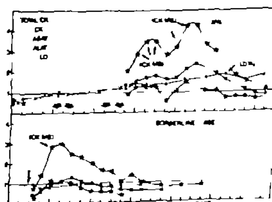


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♂ 59	Ventr fibr non AMI	120	18.6	12.0	6.6	5.4
♂ 56	Myalgic pain	138	24.6	16.2	8.4	7.2
♀ 78	Heart failure	144	17.4	10.8	6.6	5.4
♂ 76	Heart failure	192	18.0	6.0	12.0	10.2
♂ 72	Angina pectoris	360	19.2	4.2	15.0	11.4
♀ 75	After orthop surgery	540	21.0	5.4	15.6	10.2
♂ 63	Pulmonary embolism	660	19.2	3.0	16.2	9.6
♂ 39	Repeated I.M. inj.	936	25.8	4.2	21.6	12.0
♂ 25	After physic. excercise and possible viral myositis	984	18.6	3.0	15.6	6.0
♂ 56	After orthop surgery	1320	22.2	3.0	19.2	6.0

Table IV

Predictability of S-CK B

	Neg	Pos	
AMI	1	52	53
non AMI	56	0	56
	57	52	Total 109

PV Pos = 1.0
PV Neg = 0.98

Predictability of total S-CK

	Neg	Pos.	
AMI	0	53	53
non AMI	51	5	56
	51	58	Total 109

PV Pos = 0.91
PV Neg = 1.0

for 3 hours before admission (arrow) The activities of total S-CK, S-CK B and S-ASAT were only slightly increased. S-LD H_4 was not increased. On the other hand, S-CK MB was twice detected on electrophoresis. ECG indicated the possibility of a sub-endocardial *infarction but was not conclusive*. On the basis of these data, this was considered a borderline case (2)

Table III summarizes a number of non AMI cases in which subtraction of either S-AK activity measured in the individual samples or 1 per cent of total S-CK activity prevents false positive S-CK B values.

Determination of total S-CK in the diagnosis of acute myocardial infarction has the disadvantage of a low clinical specificity (2) Determination of CK isoenzymes considerably increases the specificity When using an immunoinhibition technique for CK isoenzyme analysis, the two above-described pitfalls must be taken into account to retain the clinical specificity Practically a flexible NAC activated CK reagent system including anti M is now under development by E. Merck.

The problem of clinical specificity cannot be solved by simply elevating the discrimination limit. This would inevitably lead to a decrease in the clinical sensitivity

With serial determinations performed on samples taken at 6-hour intervals, as indicated in Figs. 2 and 3 the diagnostic value of total S-CK and S-CK B was evaluated (2) This was done on a patient meterial comprising 109 non-AMI and AMI cases with an AMI prevalence of 0 49 Table IV shows the obtained predictive values of total S-CK and S-CK B

Acknowledgement

Grants from the Thorsten and Elsa Segerfalk's Foundation, Helsingborg, Sweden supported the investigation.

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Added in proof Subsequent experiments after this report was written documented that it is unnecessary to *determine* S-CK B if total S-CK is below the discrimination limit for AMI Investigations of newer batches of anti M *(1978)* have shown *that the* immunoinhibition of isoenzyme MM is so close to 100 % that the subtraction of 1 % of total S-CK is unnecessary

Bengt W Johansson. The isoenzymes most often discussed in the literature is CK MB. But LD isoenzymes are of great help in patients hospitalized late after symptoms and in order to differentiate between an LD elevation due to myocardial damage and hepatic leakage secondary to a cardiac decompensation. In addition, ASAT isoenzymes might be of value.

Accurate determination of serum ASAT isoenzymes

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Abstract

An improved electrophoretic modification for measuring aspartate aminotransferase (ASAT) isoenzymes is presented. This method fulfils the clinical requirements for sensitivity and allows the detection of 1 U/l mitochondria ASAT activity at 25°C. The procedure is relatively simple, requiring about one hour for series of 8 determinations. Mitochondrial ASAT activity was found in all patients suffering from acute myocardial infarction pathological activity was observed for several days longer than that of total serum ASAT enzyme. None of the 25 healthy people studied had mitochondrial ASAT in their serum.

Efforts have been made to use the activity of aspartate aminotransferase (ASAT) isoenzymes to confirm acute myocardial infarction. ASAT consists of two isoenzymes which, in contrast to other isoenzymes, are not specific to certain organs. One is located in the cytoplasm and the other within the mitochondria (1). The release of mitochondrial ASAT isoenzyme into the serum thus indicates the degree of cell damage caused by necrotic injury to the mitochondrial membranes. Of the several procedures proposed for the separation of ASAT isoenzymes, only electrophoresis is applicable in the clinical laboratory.

The earliest electrophoretic method which made feasible the quantitation of the isoenzymes (4 5) is too insensitive for routine use. Our new modification fulfils the requirements for sensitivity (1 U/l at 25 C) and is simple enough for day-to-day use. The procedure takes one hour and only routine reagents are needed.

The proposed method is based on an electrophoretic run on commercial cellulose acetate membranes, and the fractions of ASAT are visualized by the colour reaction with Fast Violet B. The Beckman Microzone system with barbital buffer pH 8.6 and ionic strength 0.075 M is used. The stock agar solution is made by melting 2 g agar (Difco Agar Noble) in 50 ml water in boiling bath. The solution is divided into 4 ml fractions. These are stable for 2 weeks at 4°C.

The substrate buffer contains Tris (hydroxymethyl) aminomethane, 1.2 g, L aspartic acid (Merck) 2.66 g 2-oxoglutaric acid (Merck) 350 mg, Polyvinylpyrrolidone, 3 g and N EDTA, 460 mg, dissolved in redistilled water pH adjusted to 7.4 and made up to 100 ml with distilled water. This buffer keeps for one month at 4°C.

The substrate gel is prepared by melting 4 ml of the stock agar solution in boiling water bath, mixing it with 4 ml of substrate buffer and with 0.25 ml of pyridoxalphosphate solution (KABI in tablet form, containing 0.83 mg/tablet) made by dissolving

one tablet in 1 ml of water After mixing the solution is poured immediately into a Petri dish Pyridoxalphosphate solution must be prepared immediately before use whereas the substarte gel will keep for several days at 4 C.

A serum volume of 0.25—1 00 µl, depending on the ASAT activity is applied to the cellulose acetate strips with a running time of 20 minutes at 250 V The membrane is then layered on to the substrate gel and incubated at 37°C for 30 minutes After incubation, the isoenzymes are coloured as follows another strip soaked in Fast Violet B (40 mg/1 ml of H_2O prepared just before use) and blotted slightly is layered on the membrane (which is not removed from the gel) and left for 10 minutes at 37°C The membrane is fixed by immersing in 5 % acetic acid for about two minutes, rinsing in water and drying in air The scanning is made at 540 nm with a Helena Auto Scanner (Fig 1)

The mitochondrial ASAT isoenzyme was not detectable in the serum of 25 healthy people studied This is useful result as it strongly suggests that the enzyme is present

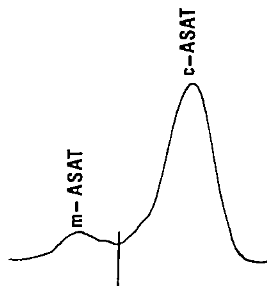


Fig 1 Representative scanning of ASAT isoenzymes of a patient with acut myocardial infarcti n Total erum ASAT 40 U/l cytoplasmatic (c ASAT) 34 U/l and mitochondrial (ASAT) 6 U/l

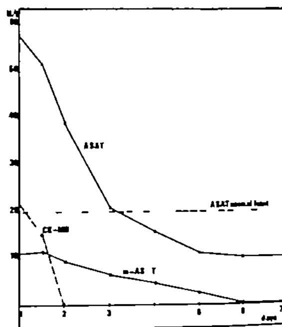


Fig 2 Daily measurements of total ASAT and mitochondrial (m-ASAT) and MB isoenzyme of creatine kinase (CK MB) in a patient having had acute myocardial infarction 24 hours earlier

only in pathological processes in the body In conformity with these findings, mitochondrial ASAT isoenzyme has not been detectable in healthy subjects by our earlier method or by more complicated and refined techniques (reviewed by Wilkinson) (6) Boyde s (2, 3) results, however derived with a semiquantitative method suggest that minimum activities of mitochondrial ASAT might be present in normal serum

We have found serum mitochondrial ASAT isoenzyme to be a very sensitive indicator of acute myocardial infarction. According to our findings, it is a considerably more accurate indicator for the detection of myocardial damage than total ASAT activity The augmentation of mitochondrial ASAT appears to take place a few hours later but remains detectable for several days longer than total serum ASAT activity (Fig. 2) Thus the determination of mitochondrial ASAT might be used to help confirm an infarct, for instance if the heart specific isoenzyme of creatine kinase (CK MB) is suspected of having disappeared from

the serum. Despite the superior specificity of serum CK-MB isoenzyme in myocardial damage, its use is handicapped by excessively quick disappearance from the serum. The determination of mitochondrial ASAT might be particularly valuable, for instance, where a negative CK MB finding is suspected of being due to delayed admission.

Because, in addition to the myocardium, mitochondrial ASAT isoenzyme is also pre sent, for instance, in the liver leakage from here into te serum might take place if mitochondrial membranes of cells ar damaged sufficiently An important point in the diagnosis of myocardial infarct is whether liver congestion is superimposed on the infarct, and whether such congestion is severe enough to cause rupture of the double membranes of the mitochondria According to our ear lier method, modest congestion of the liver was not followed by increased mitochondrial ASAT activity the serum (5) Our initial observations with the present method ha e not helped to solve this question, although massive liver damage has been observed to lead to the appearance of mitochondrial ASAT isoenzyme in the serum.

I studying highly icteric sera, an additional band is formed on the strip because conjugated bilirubin reacts with the diazonium salt. This band does not move from the application groove and is thus clearly separable from the ASAT isoenzymes The eventual clinical alue of ASAT isoenzyme determinations is still to be evaluated in further studies, for which the present sensitive and simple method appears to offer fresh possibilities.

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Creatine kinase isoenzymes in the confirmation of acute myocardial infarction

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Abstract

Serum MB isoenzyme of creatine kinase is the most specific and sensitive indicator of myocardial infarction. Despite these virtues, its clinical use is handicapped by rapid normalization after the onset of myocardial injury In patients suffering brain accidents, the increase of serum CK MB isoenzymes indicates simultaneous myocardial damage and means poor prognosis.

The conventional serum enzyme tests for confirming acute myocardial infarction have their shortcomings. The unspecificity of the tests, especially has been a challenge to the development of better methods. Since the early 1960s, it has been known that, of the three isoenzymes of creatine kinase (CK) the hybrid form (MB) is not found in significant quantities outside the myocardium

Methodological difficulties, however hampered the clinical use of MB isoenzyme in the detection of myocardial infarct. This obstacle was overcome in 1972, and preliminary findings suggested that CK MB isoenzyme might have clinical significance for confirming acute myocardial infarction (3) Since then keen research work has produced more refined methods, which have demonstrated the superiority of CK MB isoenzyme in the confirmation of acute myocardial infarct It surpasses the other methods in both specificity and sensitivity (4) The virtue of the CK MB isoenzyme determination has been verified in a large number of studies (see, e.g 7 8)

Serum CK MB isoenzyme determination is often the only enzyme test that in complicated cases, makes possible the confirmation or exclusion of necrosis in the myocardium When suspicion of an infarct is aroused, for instance, after operation, in shock, after muscle trauma, coronary angiography or cardiac catheterization, the serum CK MB isoenzyme determination offers the only reliable indicator for verifying myocardial injury

It is often difficult to differentiate between pulmonary embolism and myocardial infarction. The similarities in the clinical picture — ECG changes mimicking myocardial infarct and elevations in conventional serum enzymes — confuse the matter Moreover in connection with pulmonary embolism an anginal attack without an infarct — due to diminished coronary blood flow — could cause further diagnostic difficulties In such situations where there is no myocardial infarction, the CK MB isoenzyme remain normal (5)

The main disadvantage of the clinical use of the CK MB isoenzyme is that its activity normalizes very rapidly after myocardial infarct. This is a particular handicap where the precise time of onset of an infarct is uncertain Another problem although of minor clinical significance is that muscular dystrophies, such as Duchenne's and Becker's diseases, almost always elevate serum CK MB isoenzyme (10) evidently because of changes in the skeletal muscles (9) although a contribution of heart damage in such patients cannot be excluded. However the characteristic clinical picture, together with muscular studies, makes it easy to distinguish dystrophic patients from those suspected of suffering from myocardial infarction.

The normal serum activity of creatine kinase consists of muscle type (MM) isoenzyme the brain-type (CK BB) has only recently been discovered in the serum (1 6) This was thought not to have any clinical importance, although recent findings have hinted that it might be of diagnostic significance in cerebral accidents (1 11) Cerebral trauma and severe cerebral injuries are accompanied by a release of brain-type (BB) isoenzyme into the serum, but more local brain damage such as ischaemic brain injury elevates serum BB isoenzyme only very occasionally whereas diffuse brain damage is often accompanied by elevation of BB isoenzyme in the serum (1) The final clinical significance of the brain-type CK isoenzyme is still to be established, and the present superficial knowledge requires additional support. Acute brain damage which frequently appears superimposed by myocardial damage as indicated by ECG serum CK MB, and autopsy worsens prognosis significantly with or without serum BB elevations (2)

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Bengt W Johansson The predictive value is often given to characterize test. But when doing so, it is important to tak into consideration the pertinent patient population

Are "predictive values" from different patient materials comparable?

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I recent years, it ha become increasingly common to describe the performance of diagnostic test in clinical chemistry in terms of predictive alues (1 5) The predictive alue of positive test (PV_{pos}) in given situation denotes the probability that the patient has the illness in question. Conversely PV_{neg} expresses the probability that the patient is free from the illness. The use f PV is of value in different situations, for instance, when evaluating an ld test on new indication or adding a new test to the diagnostic arsenal.

However it is necessary to be aware of some factors that influence the predictive values of diagnostic test in given situation. This article indicates some f these factors against the back-ground of our experiences with new method for the determination of S-CK B-subunit activity in the diagnosis of acute myocardial infarction (AMI) (2, 3) W first describe model

situation when evaluating a new test in the diagnosis of AMI

The clinician classifies his patients into two groups AMI and non AMI This classification is based on patient history clinical symptoms, ECG and routine laboratory data with the exclusion of the new test in question. Fig. 1 is a model of this situation The clinician looks horizontally from left to right. The AMI-group lies above and the non AMI group below the horizontal line.

The laboratory on the other hand looks at the same diagram in a perpendicular direction from below The new test can give positive or negative values in relation to a *discriminatory limit* which can be moved (4) The clinician and the chemist meet to decide the value of the new test. The laboratory discovers that even if a positive test result will in most cases, coincide with the clinician's diagnosis of AMI the analysis occasionally fails. The term *diagnostic sensitivity* describes this situation the fraction true positive tests of all AMI cases, in the figure expressed as P P can vary from 0 to 1 A sensitivity of 0 95 will give a residual fraction 1 — P of 0 05 i e. 5 per cent false negative tests.

The *diagnostic specificity* of test is expressed as Q denoting the fraction true negative tests of all non AMI cases. A specificity of 0 95 will thus mean a correct classification of 95 per cent of the non AMI cases. The residual fraction 1—Q will correspond to 5 per cent false positive tests.

Let us now calculate PV_{pos} and PV_{neg}. To do this, we must know the values of

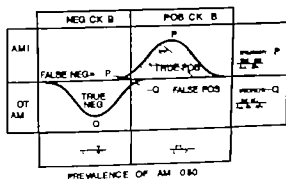


Fig 1

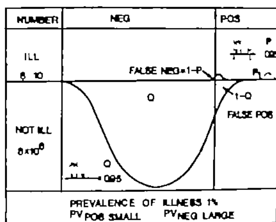


Fig 2

three primary variables diagnostic sensitivity diagnostic specificity and the prevalence of disease (AMI) in the actual population. If the AMI and non AMI groups are equal the prevalence of AMI is 0.50.

In a group of 225 patients admitted to the CCU in Helsingborg 106 were subsequently classified as AMI on the basis of traditional diagnostic criteria, corresponding to an AMI prevalence of 0 47 Serial determinations of S-CK B were undertaken in *all* patients. It was then possible to calculate PV_{pos} and PV_{neg} for S-CK B according to the simplified formulas in Fig 1

We found diagnostic sensitivity to be 0 98 and specificity to be 0 99 PV_{pos} could be calculated to 0 99 and PV_{neg} to 0 98 Thus, in our material a positive S-CK B test meant a 99 per cent probability that the patient really had an AMI

A negative test, on the other hand, meant a 98 per cent probability that the patient was a non AMI

In a different material of patients with a different prevalence of the disease, the PV_{pos} and PV_{neg} will have different values, even if the diagnostic sensitivity and specificity are the same. This might be difficult to understand intuitively Fig 2 shows an extreme situation. Let us postulate that, in a population of more than 8-million at a given time 80 000 have a certain illness and 8 million have not. This corresponds to a prevalence of the disease of about 1 per cent.

To imagine a diagnostic test in this situation with a sensitivity and specificity of 0.95 would mean 400,000 false positives (5 per cent of 8 million). The true positives, on the other hand, would be 76,000 (95 per cent of 80,000) or less than the false positives. PV_{pos} falls to only 0.16, despite the test having been performed almost as well as in our series with a PV_{pos} of 0.99.

The figure also quite clearly illustrates the problems connected to large screening investigations, with traditional tests giving about 5 per cent false positives. Only when "the ill" are markedly to the right of the healthy in the diagram can good cost efficiency situation be expected. Fig. 3 is presentation of the numerical values of PV_{pos} and PV_{neg} as a function of the prevalence maintaining sensitivity and specificity at constant values of 0.95. PV_{pos} increases with increasing prevalence of AMI. The increase

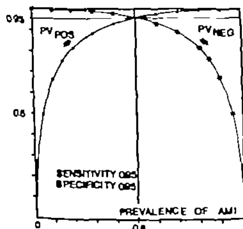


Fig. 3

is comparatively large in the prevalence area of 20—30 per cent, for instance, where PV_{pos} goes from 0.80 to 0.90. When the prevalence varies around 0.5 PV_{pos} and PV_{neg} change comparatively little.

With given prevalence of AMI and given specificity of the test, change in sensitivity will also change PV_{pos} and PV_{neg}. Fig. 4 illustrates this by looking at the results

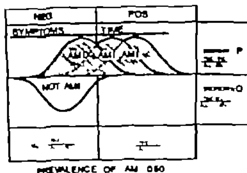


Fig. 4

of the test at different time intervals from the onset of infarction. In the diagram, the AMI-prevalence is kept constant at 0.50 and the specificity at 0.95. On admission shortly after onset of symptoms, the proportion of false negative results relatively high, the sensitivity is low and the specificity is unchanged. Both PV_{pos} and PV_{neg} are low. PV_{pos} increases as function of time to maximum value and then decreases again. This figure thus illustrates the different problems when discussing the value of the tests made either in the admission situation or later when PV_{pos} is maximum.

To revert to the original situation (Fig. 5) it can finally be mentioned that the values of PV_{pos} and PV_{neg} can obviously be manipulated by using different discriminatory limit. If this is moved towards the right, we get higher PV_{pos} but lower sensitivity and lower PV_{neg}. If the limit is moved to left, PV_{neg} increases but PV_{pos} and specificity fall.

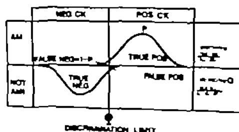


Fig. 5

To conclude, we stress the importance of evaluating PV against the patient population in question. PV from populations with different prevalence of disease are obviously not comparable without taking this fact into account. Also different diagnostic situations will influence the PV. The prevalence of AMI in the acute emergency ward will often be lower than that in the CCU. The prevalence of AMI in the CCU again, will depend on the admission policy of the CCU. The prevalence in the CCU will again be different from that of a general medicine ward. The prevalence of a given disease will thus vary with among other factors the different admission policies in different hospitals. It is necessary to take all these factors into account when comparing the PVs calculated in one patient series with those obtained in another.

Acknowledgement

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Bengt W Johansson: New diagnostic aids are of interest and importance as research tools. But are we prepared to include them in routine clinical work? Three questions are of importance in this connection.

1) How reliable are they? Do we have enough experience to use them in routine clinical practice? If so

2) What information can we get from these new methods that we cannot obtain from those available in routine work today? Are the new methods more reliable? Do we get a diagnostic decision earlier than with today's methods?

3) What are the economical consequences of the introduction of these new methods? What additional equipment and staff will be necessary for the laboratory? These expenses must be weighed against the possible profit in terms of reduced number of beds due to a clear-cut diagnosis earlier than is possible today.

These economical considerations are some of the reasons for a study we have performed in the emergency ward of the Malmö General hospital. Myocardial scintigraphy has been performed in patients suspected of acute myocardial infarction.

Myocardial scintigraphy in an emergency room

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Myocardial scintigraphy in the emergency room of the department of medicine, Malmö General hospital, was performed in 78 patients suspected of acute myocardial infarction. A mobile gamma camera (General Electric, USA) was used and 10 mCi ^{99m}Tc pyrophosphate (Diagnostics incorporated, USA) was injected intravenously. All investigations were carried out within ten hours after onset of symptoms. Th earliest examinations were made in seven cases 4 hours post-onset of symptoms and in four cases 2 hours post-onset.

All scintigrams were evaluated with regard to presence, localization, and the intensity of an uptake, and were read without knowledge of the clinical diagnosis. Each patient underwent a thorough clinical examination by a physician in charge of the emergency room. ECG and enzymes (S-ALAT and S-ASAT) were sampled twice with an interval of 6 hours. A pure clinical decision was then taken about the cause of the discomfort. When making his decision, the physician had no knowledge of the outcome of the scintigraphy

Three groups emerged

1. Those believed clinically to ha an acute myocardial infarction nd therefore referred to the coronary care unit 28 patients.
2. Those believed to have causes other than coronary disease for the chest pain and admitted to other wards n the department of medicine: 10 patients.
3. Those believed to ha any underlying cardiac disorder causing their chest pain and thus were sent home: 40 patients.

Those admitted to the coronary care unit or sent home were later re-examined scintigraphically with 1.5 mCi ^{201}Tl (Philips Duphar the Netherlands) to detect any perfusion defects.

Of the 28 patients admitted to the coronary care unit, 23 had shown pyrophosphate uptake in the emergency room. Of these, 15 were well localized and showed an intensity exceeding 1 18 of the 23 also exhibited perfusion defects when re-examined and 17 of them were later discharged with a diagnosis of acute transmural myocardial infarction. 3 were discharged with the diagnosis unstable angina pectoris the other 3 were discharged with the diagnosis other than cardiac. 5 patients, admitted to the coronary care unit, had exhibited nega ti e pyrophosphate scintigrams in the emergency room. None of these 5 later showed any perfusion defect. All were discharged with the diagnosis non-cardiac disorders.

Of the 40 patients sent home, 26 had negative pyrophosphate examinations 25 of them showed negative Tl when re-examined. The one patient with a Tl perfusion defect had suffered previous apical infarct. However 14 patients with positi e pyrophosphate scintigrams were sent home. Intensity of the uptake in only one of the 14 exceeded one. This patient later developed an acute myocardial infarction. When the 14 patients were re-examined with ^{201}Tl, it was found that 10 showed perfusion defects the other 4 had no perfusion defects (Table I)

From this study it can be concluded that myocardial scintigraphy with ^{99m}Tc pyrophosphate yields positive results, before conventional laboratory methods, which in turn might lead to other therapy being started earlier I is then possible that more myocardium can be sa ed from final necrosis.

Furthermore, negati pyrophosphate scan in the emergency room would add to the clinical confidence in sending the patients home. However a positive scintigram with an intensity above the lowest should be warning and lead to admission to a coronary care unit.

To conclude we stress the importance of evaluating PV against the patient population in question PV from populations with different prevalence of disease are obviously not comparable without taking this fact into account. Also different diagnostic situations will influence the PV The prevalence of AMI in the acute emergency ward will often be lower than that in the CCU The prevalence of AMI in the CCU again will depend on the admission policy of the CCU The prevalence in the CCU will again be different from that of a general medicine ward. The prevalence of a given disease will thus vary with, among other factors, the different admission policies in different hospitals. It is necessary to take all these factors into account when comparing the PVs calculated in one patient series with those obtained in another

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Bengt W Johansson New diagnostic aids are of interest and importance as research tools But are we prepared to include them in routine clinical work? Three questions are of importance in this connection

1) How reliable are they? Do we have enough experience to use them in routine clinical practice? If so

2) What information can we get from these new methods that we cannot obtain from those available in routine work today? Are the new methods more reliable? Do we get a diagnostic decision earlier than with today s methods?

3) What are the economical consequences of the introduction of these new methods? What additional equipment and staff will be necessary for the laboratory? These expenses must be weighed against the possible profit in terms of reduced number of beds due to a clear-cut diagnosis earlier than is possible today

These economical considerations are some of the reasons for a study we have performed in the emergency ward of the Malmö General hospital Myocardial scintigraphy has been performed in patients suspected of acute myocardial infarction.

Myocardial scintigraphy in an emergency room

Jan Lessem

Heart section, Dept. of Medicine, General hospital, MALMÖ SWEDEN

Myocardial scintigraphy in the emergency room of the department of medicine, Malmö General hospital, was performed in 78 patients suspected of acute myocardial infarction. A mobile gamma camera (General Electric, USA) was used and 10 mCi ^{99m}Tc pyrophosphate (Diagnostics incorporated, USA) was injected intravenously. All investigations were carried out within ten hours after onset of symptoms. The earliest examinations were made in seven cases 4 hours post-onset of symptoms and in four cases 2 hours post-onset.

All scintigrams were evaluated with regard to presence, localization, and the intensity of an uptake, and were read without knowledge of the clinical diagnosis. Each patient underwent a thorough clinical examination by a physician in charge of the emergency room. ECG and enzymes (S-ALAT and S-ASAT) were sampled twice with an interval of 6 hours. A pure clinical decision was then taken about the cause of the discomfort. When making his decision, the physician had no knowledge of the outcome of the scintigraphy.

Three groups emerged:

1. Those believed clinically to have an acute myocardial infarction and therefore referred to the coronary care unit 28 patients.
2. Those believed to have causes other than coronary disease for the chest pain and admitted to other wards in the department of medicine: 10 patients.
3. Those believed to have any underlying cardiac disorder causing their chest pain and thus were sent home: 40 patients.

Those admitted to the coronary care unit or sent home were later re-examined scintigraphically with 1.5 mCi ^{201}Tl (Philips Duphar, the Netherlands) to detect any perfusion defects.

Of the 28 patients admitted to the coronary care unit, 23 had shown pyrophosphate uptake in the emergency room. Of these, 15 were well localized and showed an intensity exceeding 1. 18 of the 23 also exhibited perfusion defects when re-examined and 17 of them were later discharged with a diagnosis of acute transmural myocardial infarction. 3 were discharged with the diagnosis unstable angina pectoris, the other 3 were discharged with the diagnosis other than cardiac. 5 patients, admitted to the coronary care unit, had exhibited negative pyrophosphate scintigrams in the emergency room. None of these 5 later showed any perfusion defect. All were discharged with the diagnosis non-cardiac disorders.

Of the 40 patients sent home, 26 had negative pyrophosphate examinations; 25 of them showed negative Tl when re-examined. The one patient with a Tl perfusion defect had suffered a previous apical infarct. However 14 patients with positive pyrophosphate scintigrams were sent home. Intensity of the uptake in only one of the 14 exceeded one. This patient later developed an acute myocardial infarction. When the 14 patients were re-examined with ^{201}Tl, it was found that 10 showed perfusion defects, the other 4 had no perfusion defects (Table I).

From this study it can be concluded that myocardial scintigraphy with ^{99m}Tc pyrophosphate yields positive results, before conventional laboratory methods, which in turn might lead to other therapy being started earlier. It is then possible that more myocardium can be saved from final necrosis.

Furthermore, a negative pyrophosphate scan in the emergency room would add to the clinical confidence in sending the patients home. However a positive scintigram with an intensity above the lowest should be a warning and lead to admission to a coronary care unit.

To conclude, we stress the importance of evaluating PV against the patient population in question PV from populations with different prevalence of disease are obviously not comparable without taking this fact into account. Also different diagnostic situations will influence the PV The prevalence of AMI in the acute emergency ward will often be lower than that in the CCU The prevalence of AMI in the CCU again, will depend on the admission policy of the CCU The prevalence in the CCU will again be different from that of a general medicine ward The prevalence of a given disease will thus vary with, among other factors, the different admission policies in different hospitals. It is necessary to take all these factors into account when comparing the PVs calculated in one patient series with those obtained in another

Acknowledgement

Grants from the Thorsten and Elsa Segerfalk s Foundation Helsingborg Sweden, supported the investigation

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Furthermore, negative pyrophosphate scan in the emergency room would add to the clinical confidence in sending the patients home. However positive scintigram with an intensity above the lowest should be a warning and lead to admission to a coronary care unit.

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This table shows the difference between scintigrapical results with both pyrophosphate and Thallium and discharged diagnosis

Outcome of scintigraphy		*Diagnoses when discharged*
Positive pyrophosphate positive Tl	10	1 AMI between examinations 2 old AMI and aneurysm 4 unstable angina pectoris 3 chest pain of unknown origin
Positive pyrophosphate negative Tl	4	3 unstable angina 1 chest pain of unknown origin

J Fischer Hansen What was the outcome of those patients who were sent home, but had a positive scintigraphy? Did they have an acute myocardial infarction?

J Lessem Of those sent home with a positive ^{99m}Tc pyrophosphate scintigram, two later returned with verified acute myocardial infarcts. In six patients, we also found perfusion defects when re-examined with ^{201}TL The significance of this finding is not clear It indicates that a perfusion defect is present, but its age cannot be stated. Therefore we are still uncertain whether these patients had an infarct when they came to the emergency room, but there is at least the suggestion that they might have had. The prognosis in this group of patients was unchanged

B Scherstén What was the clinical advantage of the scintigrams? Could they be used as a prognostic tool?

J Lessem To answer the first question: In our emergency ward study a negative scintigram never gave a false result. Myocardial scintigraphy could possibly result in a more rational use of CCU beds.

To answer the second question Yes, to a certain extent, but our study was not planned as a true prognostic study

P F Høilund-Carlsen What is the latest time after an infarction when the Tc pyrophosphate scintigram can be expected still to be positive?

J Lessem Usually 10—14 days after onset of symptoms. But at that late date, the intensity of the uptake is less than during the acute phase. If an aneurysm develops, a positive uptake might remain a long time after onset of symptoms.

S Persson Would you wait 10 hours after the onset of symptoms to do a Tc pyrophosphate scintigram?

J Lessem No In principle, patients with a negative scintigram can be sent home

E Sandoe Is it possible from Tc pyrophosphate scintigraphy to decide whether a thoracic pain is a sign of impending myocardial infarction?

J Lessem It is not possible to diagnose with either scintigraphy or any other method whether a true myocardial infarction will develop in these patients.

B W Johansson What are the indications for myocardial scintigraphy in the emergency ward? Is negative scintigraphy with ^{201}Tl or positive imaging with ^{99m}Tc pyrophosphate preferable?

J Lessem One indication could be to select more suitable patients for the coronary care units than has previously been done. However myocardial scintigraphy should not be used alone in deciding the future of the patients, but should only be regarded as a compliment to other investigatory methods. It is still uncertain whether ischae

mic patients can be diagnosed with either Thallium or pyrophosphate in the emergency room, but if this is so, a more aggressive therapy might be instituted earlier I the emergency room, it seems as though pyrophosphate is superior to Thallium, it cannot separate an old infarct from a new event. Re-infarcts can, for exemple, be very difficult to diagnose with Thallium.

Bengt W Johansson The ECG is often of minor help for the diagnosis of acute myocardial infarction in patients with an artificial pacemaker Myocardial scintigraphy should be of assistance in these patients, provided the tissue reaction to the electrode does not induce false positive findings. Experiences from 10 pacemaker patients without any clinical or laboratory signs of acute infarction show no positi uptake with ^{99m}T pyrophosphate, indicating that myocardial imaging is of diagnostic value in these patients.

Is determination of myoglobin in the urine or serum of diagnostic value in patients in the emergency ward or in patients seen by the doctor outside the hospital?

Bengt Schersten The methods vailable today ha not been sufficiently documented to defend their introduction in routine clinical work.

Jan Leivers A teststrip with reaction based on the ability of myoglobin, excreted in urine, to act as peroxidase has been tested in 62 patients with suspected acute myocardial infarction. Thirtyfiv developed an infarct and the strip turned positive in only 18, of whom three were positiv before ECG and enzyme rise. I 27 patients with no myocardial infarction only two positi teststrips were found. The sensitivity of the strip was thus calculated to be 52 /o, whereas specificity was found to be 93 /o.

V Hautteen Most of the discussion has concerned scintigraphy and improved enzymatic diagnosis of acute infarction. Would it not be possible to get more information from the ECG? The ECG is highly specific; it also provides a large amount of false negat findings. Is it possible to improve the diagnostic ECG sensitivity by using other leads, such as orthogonal Frank leads or vectorcardiography?

J Kyekb ECG is an empirical method, and we compare the ECG of a patient with ECG criteria considered to be normal. We will, of course, observe many false nega tive ECG As yet, we still know too littl about the forward problem relating intracardiac events to the shape of the ECG to use it as a quantitative predictor Because individual differences in the electrode distance and orientation to the infarct, differences in the geometry and conductivity of the chest, and ariations in skin resistance, quantitativ comparisons among patients are in alidated. The orthogonal leads compensate for some of these problems this offers more sensitivity in the diagnosis. Vector loop analysis takes into consideration the patial distribution of the electrocardiographic events and not only changes in peak amplitude of QRS waves.

Especially by recording the vectorcardiograms sequentially during the evolution of an infarct, small changes are readily obtained. Furthermore, multiple recordings of the vectorcardiogram can be used to construct a curve tha reflects the immediate development of the infarct. This could be of potential alue in the future.

Bengt W Johansson What diagnostic criteria should w use in the diagnosis of acute myocardial infarction? Although differences exist between hospitals, I think many keep more or less strictly to the following criteria:

1 Central chest pain, pulmonary edema, syncope or shock.
2. Appearance of a pathological Q w ve and/or appearance or disappearance of localized ST elevation followed by T wa e inversion in two or more leads of 12 lead ECG.
3 Two elevated ASAT values with a peak about 24 hours after onset of symptoms

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K. E. Green: Does S-CK and/or myoglobin increase in connection with a virus myositis and/or myocarditis?

L. Halmberg: Enzymes were not checked routinely during the acute phase in our patients with viral myocarditis, but it is conceivable that myocardial necrosis produced by a myocarditis would cause a rise in S-CK-MB.

B. Scherstén: As far as I know the literature contains no reports that give an unambiguous answer to this question.

M. Horder: From a laboratory point of view it would be advantageous if the clinicians used more strict criteria for the diagnosis of acute myocardial infarction as far as the enzymes CK, ASAT, ALAT and LD are concerned, including standardized sampling times in relation to onset of symptoms. Ninety per cent of the nordic laboratories use the standardized nordic enzyme methods for analysis of these enzymes.

G. *Biörck*: I have listened with interest to the questions and, as often happens, they have provoked some heretical thoughts in my mind. Is this refined diagnostics mainly *l'art pour l'art* or does it really mean something to our decision making for the patient? Our Chairman and Doctor Scherstén have both touched upon this matter but being somewhat older I may also have the privilege of being slightly more radical.

What does it mean in practical terms to make a diagnosis of acute myocardial infarction in a patient? Any diagnosis carries with it a prognosis (or even two) one *immediate* which may require instantaneous decisions and one *long-term* (if the patient *survives*), *implying advice with regard* to mode of life, employment, life insurance etc. — that is to say psychological loads.

Therapy depends on prognosis: in self limiting diseases with favourable prognosis therapy is often *neither needed nor* available, as in some dermatological diseases.

Now what is the difference between therapy on the basis of *symptomatology* alone, or on the basis of *diagnosis*? The function of a diagnosis is to indicate a *subpopulation* among all who appear to have a relevant symptomatology — namely those who fit a set of more or less rigid *criteria*. I would estimate that the refined diagnostics presented here might increase the size of the subpopulation by a few per cent, perhaps from 95 to 99 per cent.

But it is *per se* possible that the prognosis for the diagnostically selected subpopulation is comparable to the prognosis also for one or more *other* subpopulations who, for one or other reason, do not completely fit the criteria and thus fall outside the borders of the criteria.

Now it is conceivable that the assessment of the *clinical* symptomatology — for the experienced physician — might be as good a *prognostic* indication as that based on refined laboratory diagnostics. Could it therefore be of interest to organize further studies of the value of refined diagnostic procedures in a way that might permit a comparison with the early clinical judgement, from the prognostic point of view? I would suggest that this possibility be given consideration in the lay-out of further studies. One reason why I urge you to consider this possibility is my feeling that while *diagnosis* and *therapy* have made great progress in recent decades, *prognosis* has advanced very little — as applied to the individual case. We have massive series of epidemiological and other statistical data, but we are still very much at loss when judging the specific individual patient. In our department, we have for some time engaged in a project of early "clinical" prognostication in acute myocardial infarction by physicians and nurses in the CCU and we hope that the experience derived from a comparison of our "bets" with the later verification by the patients' fate might help to *improve our* ability to make proper prognostic judgements.

in combination with a peak ALAT value about 36 hours after onset of symptoms and lower than the ASAT peak. Alternatively one elevated ASAT value in combination with one elevated LD value with a peak about three days after onset of symptoms.

4 Myocardial necrosis at autopsy of an age corresponding to the onset of symptoms.

Criterion 4 or a combination of two of criteria 1 2 and 3 are necessary for the diagnosis of acute myocardial infarction.

Are we prepared today to revise or change these diagnostic criteria?

S Hofvendahl We use the following routine. S-CK and S-CK MB three times a day S-ASAT and S-ALAT once a day and S-LD once a day until maximal value has been passed. S-CK MB and S-LD isoenzymes provide a cardiospecific enzyme combination that covers a maximum time interval. In addition, S-ASAT and S-ALAT have a place in the diagnostic arsenal they are well documented and not costly They provide a simple estimate of the degree of possible liver involvement, which is of clinical value. Furthermore, it is possible that microinfarctions are more readily diagnosed with the sensitive S-ASAT than with other methods.

A Pedersen Based on the enzyme findings in 1300 patients out of whom 900 had an acute myocardial infarction, our routine in Glostrup has included only S-CK MB, unless there is reason to suspect that the infarction occurred more than 36 hours before the blood sample is taken. If so we determine in addition S-ASAT S-ALAT and S-LD and in selected cases an LD electrophoresis is done.

S-CK MB is analysed electrophoretically The MB fraction can be completely isolated, and the specificity is close to 100 %.

This routine requires certain laboratory efforts, but the laboratory is also relieved of the other enzyme analyses, and the necessary costs are certainly lower than for myocardial scintigraphy

E Lorentzen As the S-CK peak is of shorter duration than that of S-ASAT is it not reasonable to prefer S-ASAT? We still have little experience of the new methods. New sources of error still appear This is true, for example, in the serial determination of S-CK for evaluation of infarct size (Editorial Circulation 52 1 1975) I will therefore make a plea to wait to include these new methods in the routine diagnosis of acute infarction until we have gained more experiences and well founded results showing that they actually represent true progress.

C Müller Is there any place for S-CK MB in the diagnosis of acute myocardial infarction during or after cardiac surgery? Previous methods including enzymes are often unreliable. Is there a difference in the S-CK MB response after an uncomplicated cardiotomy and an aorto-coronary by-pass? Can an increase of S-CK MB postoperatively be regarded as an expression of an acute myocardial infarction?

S Ström Frequent CK MB determinations in 25 consecutive cases of coronary by-pass operations with mammary artery or saphenous vein show that CK MB in serum is found in all patients postoperatively with a wide range of maximum values. Myocardial infarction could not be diagnosed in *any of these* patients with conventional methods and the CK MB curve postoperatively differs from that seen after an infarction with a maximum in direct connection to the operation. Drainage of the right atrium, which is routinely done during these operations, produces myocardial damage, but it is small and should be of the same magnitude in all patients. There is a correlation between CK MB level and the duration of extracorporeal circulation and aortic clamping, that is to say between enzyme release and the amount of ischaemia.

J Lessem Tc pyrophosphate scintigraphy is of great value in the diagnosis of per and postoperative myocardial infarction.

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Bengt W Johansson It is often difficult to get a definite diagnosis in patients who die soon after the onset of symptoms. An autopsy might reveal a pulmonary embolus or a cerebral haemorrhage. An acute myocardial infarction takes several hours to produce clear-cut gross or microscopical changes. Half of the patients leaving hospital after treatment of an acute infarction die suddenly This can be due to a ventricular fibrillation without an infarction it can also be due to an acute infarction, and the time might have been too short for a coronary thrombus to develop The coronary circulation during ventricular fibrillation will drop to almost zero with subsequent myocardial changes. It takes some time for the infarct to become manifest, although a decrease in potassium and an increase in sodium and calcium concentrations have been reported to occur a few minutes after the coronary circulation has stopped. These problems are especially relevant in forensic medicine.

The diagnostic of fresh ischaemic lesions in forensic pathology

Gerhard E Voigt

Dept. of Forensic Medicine, University of Lund, LUND SWEDEN

Sudden and unexpected death dominate the autopsy material of Departments of Forensic Medicine Heart disease is the most common cause. By gross examination, it is difficult to differentiate such cases from intoxications with medicaments such as sleeping pills, tranquilizers, or analgetics, often in combination with alcohol These intoxications do not cause specific morphological changes and can easily be overlooked, as can an early myocardial infarction To select the cases demanding toxicologic chemical analysis, it is most important to have methods to verify the early stages of myocardial ischaemia, indicating that the cause of death was cardiovascular

In our experience the heart dissection technique during autopsy is important for visualizing early stages of infarction. Thus the left ventricle is opened by a cut at the left margin of the heart running through the mitral valve. From this cut, another is made with scissors to the aorta, leaving a small part of the wall of the left ventricle between the two cuts. The wall of the left ventricle is then stretched open and its thickness is halved, beginning at the apex of the heart and continuing to the level of the coronary sulcus. It is important not to wash the heart before investigating the cut curface A fresh infarction has a prominent cut surface, but there is often no difference in the colour between the ischaemic and non-affected parts of the muscle. It is almost impossible to see fresh infarctions on small cut surfaces. Concerning further investigations to verify fresh myocardial infarction Knight has recently surveyed reliable methods. He recommends for the most part histochemical enzyme methods (malate dehydrogenase) and describes SDH and LDH as useful tests. For two reasons, we cannot use such methods as routine tests

1) Many of our cases have a variable degree of autolysis making it impossible to obtain reliable results, 2) For a department with a large autopsy load (2200/year) and a small medical and technical staff the histochemical methods are too time-consuming Thus, we need simple methods that provide reliable results also on decomposed material

At our department, the Mallory PTAH stain has been chosen to visualize ischaemic myocardial lesions that can be overlooked

in haematoxylin and eosin stained slices. We have used this method for about 12 years in several thousand cases. To achieve satisfactory staining results, the following is necessary:

1 The tissue pieces preserved at autopsy for fixation in a 6—10 per cent formalin physiological saline solution must not be much larger than the later paraffin embedded material. The volume of the fixative must be more than 20 times that of the tissue. In microscopic sections from material fixed in o ersized pieces and in too little formalin, the PTAH-method, excepting marginal areas, stains the muscle fibres reddish instead of intensive blue-violet.

2. 2 per cent potassium permanganate and 1 per cent oxalic acid solution must be freshly prepared before use.

With this method, the first sign of an ischaemic lesion is a patchy change in the width of the normal striation. In later stages, there appear broad bands and granules with deep blue-violet colour which contrasts well with the reddish-stained cytoplasmic background. Later these bands and granules disappear and the injured muscl fibres stain only red. In this stage, inflammatory cell infiltration is often visible.

This method allows no more to be seen than in haematoxylin and eosin stained sections, but the PTAH method makes it easier to detect ischaemic lesions and affords considerabl security in the microscopical analysis. I material decomposed by autolysis, the PTAH-method, in our experience, is the stain of choice, especially when haematoxylin and eosin staining does not give reliable results.

A ascular dependent hypoxaemia or ischaemia does not, in general, result in immediate morphological changes. I fresh infarctions, there are nearly always various stages of change in groups of myocardial fibres. Thus if in case of sudden unexpected death, some groups of changed muscle fibres are found in the sections, this strongly indicates that death was due to cardiac causes. This finding must, of course, be interpreted in relation to the other autopsy findings. A ery important finding is haemorrhage in an arteriosclerotic plaque. Thrombosis in cases of fresh ischaemic lesions occurs only exceptionally

Another method of visualizing fresh ischaemic myocardial lesions, discussed several times in the literatur is the HBFP (haematoxylin basic fuchsin-picric acid)-stain according to Lie *et al.* The method seems to be technically easy to perform. In improving upon this method, the following observations ha been made:

If a series of sections of the same material are stained on one slide, and the slide in the different baths remains upright, difference in the staining result occurs between the sections on the top and those on bottom of the slide. This indicates that the method does not quite give reproducibl results.

In the method according to Lie, the sections are transferred after staining in an aqueous basic fuchsin solution to water to acetone, and to a bath consisting of picric acid and acetone, where the red colour (basic fuchsin) runs off the sections. It is desired that only the muscle striations within ischaemic lesions remain stained.

According to this method, the sections are not dehydrated before treating with acetone-picric acid. It can be supposed that water-free picric acid extracts the dye-containing water from the sections. If the sections, after staining with basic fuchsin, are dehydrated by drying with filter paper and immersion in baths of methyl benzoate (which extracts only water and leaves the dy in the section) followed by treatment in xylol acetone and afterwards immersed in solution of water-free picric acid acetone, the decoloration of the section takes som time. But this process can be quickly expedited if the sections are removed from the bath, hydrated with breath moisture, and quickly returned to the solution. Thus it would appear that the water content of the sections is the most important factor in achieving the desired results. Ischaemic muscle fibres probably have a greater density than uninjured muscle fibres. The affi-

nity of the ischaemic structures to water containing fuchsin is thereby somewhat greater than the affinity of uninjured structures. But the difference between the affinities is so small that it seems impossible to carry out the method in such a way that only ischaemic lesions can be visualized. This method is therefore of no value in the routine work.

To summarise The PTAH method, if handled technically correctly is in our experience the method of choice with which easily to visualize fresh ischaemic lesions in the myocardium.

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The Ustaoset Hypertension Meeting 1978

Report from the 9th Nordic Hypertension Meeting
in Ustaoset, Norway April 13-14 1978

Edited by Per Lund-Johansen

Distributed by The Almqvist & Wiksell Periodical Company Stockholm, Sweden

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INTRODUCTION

This symposium represents the 9th in a series of meetings between hypertension researchers in the Nordic countries Denmark Finland Norway and Sweden At the last meeting in 1976 it was decided to publish the abstracts from these meetings and the first report appeared in Acta Medica Scandinavica Supplement 602, 1976 edited by Lennart Hansson Sweden The great interest in reprints from this volume have convinced the organizers that also the abstracts from the following meetings should be published This is the second report in this series

The Organizing Committee (Denmark Jørn Giese Tage Hilden Hans Ibsen Finland Antti Eisalo Pentti Halonen Heikki Karppanen Norway Harald Aars Per Lund Johansen Haakon Storm Mathisen Sweden Lennart Hansson Bertil Hood Bengt E Karlberg) wishes to express its gratitude to the Scandinavian division of Merck Sharp & Dohme who through a generous grant made this meeting and the printing of this volume possible We would also particularly thank MSD Norge A/S by director Per Wold Olsen and Mrs Ellen Wright Kristoffersen for invalu able technical and secretarial aid

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HEMODYNAMIC INVESTIGATIONS ON RELATIVES OF PATIENTS WITH ESSENTIAL HYPERTENSION

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Many ttempts have been made to find early hemodynamic changes in patients with essential hypertension The basi f these studies has mostly been patients ith borderline or labil hypertension (1 2 3 4 5 6 7 8)
Our basi has been genetic By examining rel tives of patients ith ess hypertension we have had possibility to study the problem in very early stage

MATERIAL:

The material consists of 76 patients with essenti l hypertension who were treated t the hospital They all had inf rmed us that a least one person in the last two generations had suff red f rm the disease Hypertension was also assumed t exi t in family members suffering from cerebrovascula incidents before the age f 60 years Presence of diabetes r secondary hypertension mechanisms like renal artery stenosis was disqualifying f r this tudy
From the 76 persons we received anamnestic data bout 801 rel tives We were informed that about 50 % f these rel tives probably had suff red from essenti l hypertension r sequeles f this disease
The rel tives who were still live and had no known hyp rtension were call d to hospital fo examination 255 relatives re accounted fo in this tudy 31 f these relatives have been examined with invasive hemodynamic investigations including contionuos blood pressure registra tion and det rmination f cardiac output during various provocationtests
19 volunteers without known hypertension in their families have been used as a controlgroup
53 rel t ves and 25 control have been investigated in regard to plasmavolume at est

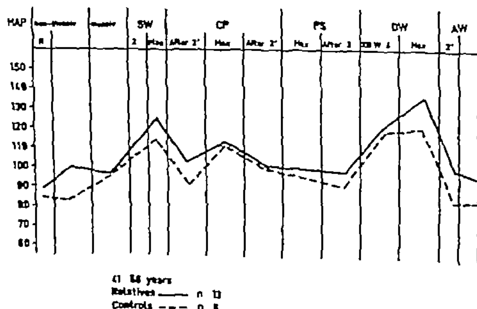
	N	DBP	HR	CI	PRI
Relatives	31	78 8	68	3 3	30 8
Controls	19	74 0	69	3 6	28 1

(N=number DBP Diastolic blood pressure HR Heart rate CI Cardiac index PRI periferal resistanc index)

The periferal resistance is about 9 % higher in the relativ group Subdi iding the group into the ages 20-30 30-40 and over 40 one can find that in the latter age group there are five persons who have a lower cardiac output and consequently a higher perif ral resistance that their controls despite a diastolic blood pressure which is identical with that of their controls

As a whol there are no differences between the relatives and the control in regard to the maximal blood pressure during the provoca tiontests Relatives in the olde t age group however do differ from their control in this parameter

(Fig 1)



(R rest P pain SW tatic work CP cold pressure PS p ychical tress DW dynamic work AW after work)

METHODS:

All blood pressures were measured by the same nurse The patients rested in supine position for 10 minutes before the reading Korotkoff sound phase 5 was used for determination of the diastolic pressure The blood pressure was measured in both arms the higher then recorded for this investigation

The invasive investigations were performed at the dept of Clin Physiol The patients came after fasting to the laboratory in the morning A catheter (PE-160) was inserted percutaneously to the right atrium under x-ray control Another catheter of the same size was inserted in the brachial artery after previous anesthesia The tip of the catheter was placed in the axillary region The cardiac output was determined with the dye dilution technique using bromsulphtalein as indicator substance Plasmavolume was determined by Evans blue after 15 minutes equilibriation The central plasmavolume was calculated from the dye dilution curves using the formula: mean transit time (MTT) x cardiac output (CO) (ref 9) The periferal resistance was calculated by dividing mean arterial pressure (MAP) by CO During continuous intraarterial blood-pressure registration the following provocation tests were performed pain stimulus during insertion of the catheter into the antecubital vein static muscle work at 30 % of the individual maximal capacity during five minutes cold pressure test during 2 minutes psychical stress with a binary choice generator and dynamic work up to maximal capacity All tests were pere formed with the patient in supine position Cardiac output was determined in the middle of all the above tests excluding pain-stimulus During dynamic work with a ergometer cycle we determined cardiac output after 2 minutes at 50 and 150 Watt

RESULTS

We chose to use the Humerfeldt study of the inhabitants of Bergen (10) as a reference for expected blood pressures in various age groups We found that 65 % of our relatives have a blood pressure which is higher then expected for their age

It was decided that one normotensive member of each family should undergo the invasive examination As a controlgroup we used an age and weight matched group without known hypertension in their families Table 1 shows the basal data in the two groups:

pressure and high perif ral resistance In our mat ri l the plasma volume is lower without correl tion to diastolic blood pressure or periferal resistance

The explanation f these results can only be speculative One hypothesi is that the relatives have highe sympathetic tonus with subsequent constriction in the postcapillary venules and in the venous reservoirs The lower plasmavolume could be an adaption to the restriction f these vessels Preliminary data from our investigations (21) on the sodium metabolism f the relatives shows an lt red i tracellular sodium metabolism wh ch could result in increased sensibility to catecholamines (22) It is also possibl that the normotensive rel tive have lready begun to acquire arte al l sions cau ing ltered sen-siti ity in the kidneys volume receptors Lastly the relatives could have occasional blood pressure levat ons with a highe transcapill ry escape

Othe authors have found circul tory lterations in early and persi tent hypertensive indiv duals Ou data from an heredita ily prone material consi ting of relatives f hype tensive patient testifi to the existance of irculatory alterations even in normotens ve condition These results motivate f rthe genetic-o iented investigations of hypertensive famil es in orde to bett r define hemodynamic and metabolic changes in the earlier stages of hypertension

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The total plasmavolume and hematocrit of 53 relatives and 25 controls was also calculated Although the hematokrit was the same in both groups the relatives as a whole had a significantly lower ($p < 0.001$*) plasma volume than their controls: 15 8 versus 19 0 ml/cm height The difference was accentuated in the 20-30 age group where the plasmavolumes were 15 6 versus 19 8 ml/cm The mean diastolic blood pressure for this age group was 80 mm Hg for the relatives and 75 mm Hg for their controls The mean for the entire material was a little higher: relatives 83 mm Hg versus controls 78 mm Hg

DISCUSSION

There seems to exist some hemodynamic differences between normotensive relatives in hypertension prone families and a control group without known hypertension in their families In this study we have found significant differences in regard to total plasmavolume between the two groups There is also a tendency to a higher central shift of the plasmavolume during dynamic muscle work A subgroup of the relatives show a higher blood-pressure response during muscle work

Follow up studies of persons with borderline and labile hypertension present very diverging results ranging from no higher risk of disease manifestation to double the risk Our anamnestic data shows that eventu ally persistent hypertension appears in about 50 % of the families Contrary to several studies in borderline hypertension (2 3 4 5 6 7) we have not found any signs of hyperkinetic circulation Conceivable mechanisms behind the high cardiac output sometimes found in borderline hypertension data include a primary disturbance in the myocardium (11) vagal inhibition (12) and sympathetic hyperactivity One hypothesis is that sympathetic hyperactivity could cause a diminished capacitance volume with increased central plasmavolume and cardiac output

Safar (13) Tarazi (14) Ulrych (15) find higher central plasmavolume in patients with borderline and persistent hypertension The correlation exists however only during simultaneous presence of high cardiac output Other authors have found lower plasmavolume in hypertensives (16 17 18 19 20) The referred materials are inhomogenous consisting of all stages of hypertension including borderline and persistent hypertension In some borderline groups one has not only found a significantly lower plasma volume in comparison to a normotensive controlgroup but also a correla tion between lower plasmavolume and a slightly higher diastolic blood

HEMODYNAMIC AND HORMONAL CHANGES INDUCED BY NOISE

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Abstract Eighteen healthy mal volunteers with normal hearing were exposed to industri l noise t different sound levels (75 85 and 95 dB A) i noise laboratory Blood pressure heart rat stroke volume and card ac output were recorded w th non-invasive techniques Adrenaline and noradrenaline concentration in venous plasma were analyzed before and during noise exposure The mean resting blood pressure of the whol group was 120/70 mm Hg During noise stimul tion diastoli blood pressure increased (12 2% $p < 0.001$) as did mean arterial pressure (6 6 $p < 0.001$) and total peripheral resistance (12 7% $p < 0.001$) Stroke volume (7 3% $p < 0.001$) and cardiac output (5 0% $p < 0.01$) were both reduced at 95 dB A

Heart rate and systolic blood pressure did not change significant ly At 75 and 85 dB A there were similar but smalle changes in the hemodynamic parameters

There were no changes in adrenaline and noradrenaline in plasma during maximal noise exposure

The noise induced hemodynamic changes remained 5 inutes fter the noise timulation was topped but had disappeared after 10 minutes f rest

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D p rtment of Hygiene University of Göt bo g nd
H l AB Göt b rg Sw den

Abstract Eighteen healthy male volunteers with normal hearing were exposed to industr l noise at different sound levels (75 85 and 95 dB A) i noise laboratory Blood pressure heart te troke volume and cardiac output were recorded with non-invas ve techn ques Adrenaline and noradrenaline concentration in venous plasma were analyzed before and during noise xposure The mean resting blood pressure of the whole group was 120/70 mm Hg During noise timul t on diastolic blood pressure increased (12 2% p < 0 001) as did mean rteri l pressure (6 6% p < 0 001) and t tal peripheral resistance (12 7% p < 0 001) Stroke volume (7 3% p < 0 001) and cardiac output (5 0% p < 0 01) were both reduced t 95 dB A

Hea t rat and systoli blood p essure did not change significant ly At 75 and 85 dB A there were imila but smaller changes in the hemodynamic paramet rs

There were no changes in adrenaline and noradrenaline in pl sma during maximal noise exposure

The noise induced hemodynamic changes remained 5 minutes after the noise timulation was stopped but had disappeared fter 10 minutes of rest

It has been known for several decades that noise can cause temporary blood pressure increments in animals e g different strains of rats In 1948 Yeakel et al (1) showed that daily noise exposure to rats for several months resulted in a blood pressure increase which remained for four months after the noise stimulation had stopped Furthermore they showed that if the animal was reexposed to noise the blood pressure increment came faster than during the initial exposure indicating a mechanism of sensitation in the animal

Several studies have shown that different stress stimuli e g noise can produce temporary blood pressure increments in SHR-rats and that these stimuli accelerate the development of permanent hypertension (2 4-7) Jonsson and Hansson have shown that industrial workers with a severe noise induced hearing imparment (defined as more than 65 dB A hearing loss at the frequencies 3000 4000 or 6000 HZ) had significantly higher blood pressure compared to an age-matched control group with normal hearing (defined as less than 20 dB hearing loss at any frequency); 8 Furthermore in the group with noise induced hearing loss there were significantly more hypertensives compared with the control group (8) This made us interested in further evaluations of the effect of noise on blood pressure and other hemodynamic variables Thus the aim of the present study was to investigate the hemodynamic and hormonal effects of acute noise stimulation in man

PATIENTS AND METHODS

Eighteen male healthy volunteers with normal hearing (audiometry) participated in the investigation Their mean age was 26 years range 23-31 They were studied in the afternoon under strictly standardized conditions in a noise laboratory Following 20 minutes rest in the supine position at a sound level of 40 dB A noise stimulation started The patients were divided into two groups The first group (n 8) was exposed to increasing noise levels in 10 minute periods starting with 75 dB A followed by 85 dB A and 95 dB A The other group (n 10) was exposed directly to 95 dB A for 20

with sound levels up to 105 dB A The he odynamic parameters wer recorded veral tim s bef re during nd fter the nois sti l tio Adrenaline and noradre aline in venous pl s were studied after 20 minut s rest in th upine position and after 5 min tes of noise p sure t 95 dB A The subjective experi nc of the ise disturban s was registered ı a questionnaire The inv tig tion was ended by resting p riod at 40 dB A

Blood pr ssure was measured indirectly with n a tomatic blo d press re record r (Bosch B so at) There w s a v ry g od orrel tion (r 0 93 p < 0 001) between simultaneously recorded bl d pre sur s with a er ury man meter nd the tomatic bl od pr s re rec rder Diast lic blo d pr ssure s m sured t th disappe rence f th Kor tkoff sounds (ph se V) H rt r te and troke volum were rec rded on ın sively ıth imped nce c rdıogr phy (9) Its orrelatı n th dye dilution techniq e (Cardio Green) was r 0 89 p < 0 001 (13) It is kno n to b at least as reliable as th dye dil tıon t chnique as easi g ch ng s ın stroke lum in th s me per o (10 12)

Tot l p rıph ral resi t nc was al ulated s the quoti nt of m n rt rial blood pre sure nd ca disc o tp t The blo d ples for c tech lamine a alysi (13) wer t ken fr m c nul ın rt d in n nt ubital in 10 minut s b fore the est g p rıod st rt d

RESULTS

At 95 dB A ther e s highly ıg ificant ın r ments in dı st lic bl od pre sur (12 2% p < 0 001) an art ri l pr e s (6 6% p < 0 001 nd total perıph ral resiste c (12 7% p < 0 001); Fig 1

The tr ke ol d cr s ed sıgnıfı ntly (7 3% p < 0 001) s did th c rdıa tput (5 0% p < 0 01) H rt rate s d y tol c blo d pr ss r dıd not change sig ificantly

At 75 dB A there were tat stically ignific nt in rements in dı st lic bl od pres u e (5 0% p < 0 05) me n arterial p e (3 2% p < 0 05) and total perıpheral resistanc

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di turb c and bjectively c rded hemodynamic changes

Th hemody amic cha ge w re still pre ent 5 minutes after the oise stimul tion was stopped b t they had dis appeared after 10 minutes of quiet r st at 40 dB A

Th r r no signific nt ch nges in adrenaline or r adre line c nc ntration in plasma during m ximal n is sti ulation (95 dB A) nor were there any correl ti n bet e n th hange in h m dynamic pa ameters and the cate- ch l ine concentrations

DISCUSSION

Ac te nois exposure ca s d temporary blood pr s re incre se i normal lunteers Th blo d pressure increase as ssoci ted th increa ed to us in the res st n e ess la dicated by the i resists This was re er ibl hen th noise timulation w s stopped The decrease in stroke olume nd c rdia o tput co ld be seco dary t b ror ptor efle a t ity W d d n t find a lin r r lati nsh p bet noi le el and blood pressur incre s nc ll h odyn mic chang s ith the e cept on of th s reg rding st oke ol me a d card o tput w le pron no d at 85 dB A c p red ith 75 dB A

Ther c ld be ver l different reason for th The br pt ch ng in so nd l l fr m th v ry q iet 40 dB A to 75 dB A is pr portion lly great r ch nge in noise l vel the th ch g fr 75 dB A t 85 dB A

An th r po ibl e pla ti c ld b that the tial he odyn mi ch nges t 75 dB A might b second ry t co bi t o of the oise xpo r d pect ncy tres

Th r re different pinion r ga d ng chron o pos r and its p s ible as ci ti with pe m ent hype te si n in man (8 14 15)

Se r l f t rs ld modify th c rd as lar r sp n e to n i e in m n e w ll e in n m l R peat d d ily pos e to o se f r l ng p ri d c uld oncei bly re t a p r t hype te s o in m n d to st uctu l ha ges th re stance e l i logy ith findi g i animal studie (7)

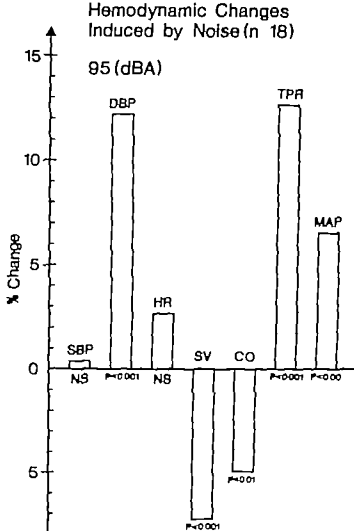


Fig 1 Hemodynamic changes in 18 healthy subjects caused by noise stimulation at 95 dB A

(11 1% p < 0 05) Heart rate (3 2% n s) stroke volume (3 6% n s) systolic blood pressure increased (1 1% n s) and cardiac output (6 2% n s) did not change significantly

At 85 dB A there were changes similar to those at 75 dB A although they were less pronounced

There were no significant differences at 95 dB A between the group which was exposed to a step wise increase in noise and the group which was directly stimulated with 95 dB A

Loud short intermittent noise (105 dB A) did not accentuate the hemodynamic response elicited by continuous noise at 95 dB A

There was no correlation between subjectively experienced

Primary hyperten ion r fractory to tripl drug t eatment a tudy on cent al and peripheral hemodynamic

by

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Hemodynamic factors involved in blood p ess r eg l tion wer inv tigated in te hyperten ive patients f actory to the combined t eatment with diuretic (hydrochlorothi zide 50 mg daily o bendroflumethiazide 5 mg daily) prop anol 1 120 160 mg t i d and hyd l zine 50-75 mg t i d The patients wer compa ed t ten othe hyperten si patients matched for sex ag weight glomerular filtration te and l iti l unt eated blood pr su e esponding adequat ly to the co esponding the apy On the t iple the py de ibed used fo mo e than two years none f the r f actory patients had mean rterial p essure ed ction of 10 % o mo e no were thei blood pre sure below 200/110 mm Hg t the cli ic The responding patients had ed tion of mean arte ial pressu e of 20 % mo and blood p s s below 180/100 mm Hg t the cli ic The patients i each pai had the same drug and doses and they we e checked fo drug defa lting (1) All the twenty patient had high degree f β-ad eno ecepto blockade judged from isoprot enol i fusion (1) The ten patients i the fractory group wer low acetylato f hyd lazine whil five of the responde s we f t c tyl tors The patient i both groups had p imary hype ten ion and ll had eye-ground changes g ade II (K W B) Cardi c output was det rmined with dye dil tion technique (indocyanine green) and pl sma volume with E ans Blue Blood flow nd vascul sistance t rest and t maximal vasodil tation i a skin (hand) and muscle (calf) vascul r bed we det rmined using venous occl sion plethysmog aphy and i t art ial and auscultatory blood pre re recordings spectively Maximal vasodilatation was obtained by direct and indirect heating a t ri l occlusion and digital work (hand) by te ial occl ion and muscl work (calf)

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P imary hype tension ref actory to t ipl drug treatment a study on central and pe iphe l hemodynami

by
Ove Andersson M D Lennart Hansson M D and Ramon Sivertsson M D

Depa tment of Medicine I and Depa tment of Clinical Physiology II
University of Götebo g Göteborg Sweden

Hemodynami f ctors involved in blood p essure regulation were investigated in ten hypertensive patients r fractory to the combined t eatment with diu etics (hydrochlorothiazide 50 mg d ily or bendroflumethia ide 5 mg daily) propranol l 120-160 mg t i d and hydral ine 50-75 mg t i d The patient were compa ed to ten other hype ten sive patients matched f r sex age weight glomerula filtration rate and i itial untreated blood p essu r sponding adequat ly to the corresponding the apy On the triple therapy des ibed ed fo mo than two years none of the r f ctory patients had a mean a teri l p ssu reduction of 10 % or mo e no wer their blood pres sure below 200/110 mm Hg t the cli i The esponding patients had eduction of mea rt ial p ss e of 20 % or more nd blood p e su below 180/100 mm Hg t the cli ic The patients in each pair had the same drugs and doses and they were checked f r drug d faulting (1) All the twenty patient had high deg ee f β adrenoreceptor blockade judged from isoprot enol inf ion (1) The ten patient i the ef ctory group we slow acetyl to s of hyd alazine whil fi of the esponder we e f st c tylato The patients in both group had p imary hype tension and all had eye-ground chang s grade II (K.W B) Ca diac output we determined with dye dilution technique (indocyanine green) nd pl sma volume with E ns Blue Blood flow and scul re istance at t and t ma imal sodil t tion in ki (hand) nd muscl (calf) scula bed were det rmined sing venou occl sion plethysmog aphy and i tr arte i l and auscultatory blood p ess re recordings espectively Maximal sodil tation wa obtained by direct and indirect heating rte ial occlusion and digital work (hand) by t ial occlusion and muscl work (calf)

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P imary hyperten ion refractory to tripl drug treatme t study on cent l and peripheral hemodynamics

by

Ove Ande son M D Le nart Ha sson M.D and Ramon Slvertsson M D

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The refractory patients had increased total peripheral resistance in comparison with the responders (Table 1) while cardiac output and plasma volume did not differ between the groups This suggests that the increased peripheral resistance is the important factor for the sustained blood pressure elevation during the influence of the actual therapy Furthermore in comparison with the controls the refractory patients had increased vascular resistance at maximal dilatation (Table 1)

Table 1 Central and peripheral hemodynamics in refractory patients and patients responding to triple drug therapy

	Central hemodynamics			Peripheral hemodynamics			
	MAP mm Hg	CI ml/min m²	TPRI U/m²	Resistance at max dilatation hand PRU_{100}	calf PRU_{100}	Resting tone hand	calf
Refractory patients	119	2 72	45 9	3 6	3 9	2 7	14 8
Responding patients	94^{xx}	2 70	$35\ 6^{x}$	$2\ 8^{x}$	$2\ 9^{x}$	2 8	13 5

This indicates a vascular abnormality in this group (2) Since the dilatation procedure abolishes smooth muscle tone in the resistance vessels almost completely the vascular abnormality is interpreted as a structural change most likely an adaptive thickening of the vessel wall associated with hypertension (3 5) The results indicate that this abnormality is more pronounced in the patients refractory to treatment

The ten patients refractory to therapy were then treated with minoxidil (15 35 mg/day) as the only vasodilating agent with the propranolol dose kept constant and the diuretic ther py kept almost contant (increased i one patient) After the change in therapy all ten patients had a eduction f blood pressure below 170/100 mm Hg at the clinic within two months The blood press re reduction was co el ted to an increase in resting blood flow A modest increase i plasma volume was noticed

No change in the resistance t maximal vasodil tation was found Consequently no sign of eversibility of the vascular abnormality was demonstr ted aft r two months of blood press re lowering therapy (4)

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(HOE 118) where blood pressure cardiac output and peripheral vascular resistance had been monitored during the determination of therapeutically acceptable dosage we have taken the opportunity of comparing these haemodynamic parameters under a pure diuretic treatment and under a combination of diuretic with beta-blocker in the same patie ts The patients were on n average rather young ($\bar{m}$ = 40 years range 20–59) ll with a mild hypertension

The plan of the assay was as follows:

Placebo 2 weeks – HOE 118 in growing dosages 6 weeks – placebo 2 weeks – Baycaron + Inderal 6 months

Blood pressure and cardiac output have bee examined and peripheral vascular resistance calculated one or more times during each period Average parameters for the placebo pe iod for highest dosage of HOE 118 nd for maintenance dosage of Baycaron + Inderal have bee compared Cardiac output was determined by an impedance cardiography method (Kubicek et l 1966 Minnesota Impedance cardiograph model 304 A) Differences have been evaluated by a Student s t-test for paired compa isons and by a sign test estimating whether the relative numbers of positive and negative differences betwee treatment periods may be ascribed to chance

Table I gives the average values of body weight blood pressure heart rate cardiac output and peripheral vascular resistance All parameters have bee determined supine and standing The blood pressure is sig ificantly lowe under HOE 118 than unde

HAEMODYNAMIC PARAMETERS IN HYPERTENSIVE PATIENTS TREATED WITH A DIURETIC AND WITH A DIURETIC IN COMBINATION WITH A BETA-BLOCKER

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Odense University Hospital Odense Denmark

Treatment of mild arterial hypertension with a thiazide diuretic as the only antihypertensive drug is well recognized In Denmark the majority of hypertensive patients taken care of by their practitioner are treated in this way In our out-patient department however we have for a couple of years used a combination of a small dosage of mefruside (Baycaron®) with a small dosage of propranolol (Inderal®) in mild hypertension The most commonly used dosage has been 25 mg of mefruside and 40 mg of propranolol taken together in the morning Especially in younger patients this treatment has proved satisfactory

In connection with the perusal in 12 hypertensive patients (9 males 3 females) of a new loop diuretic related to furosemide

lowering seems primarily to be brought about by a reduced cardiac output whereas n significant differences of the calculated peripheral vascular resistance could be demonstrated In the standing position the pulse rate is higher for alle types of treatment the pulse amplitude I smaller the cardiac output is lower and the peripheral vascular resistance is higher

The body weight is significantly reduced under HOE 118 This is probably due to dehydration and the weight loss is regained under Baycaron + Inderal

It may be concluded that under a combined diureti + beta-blocker regimen with very small dosages of both types of drug a more pronounced blood pressure lowering may be attained without dehydration without postural hypotension and with no higher peripheral resistance tha unde a rather massive diuretic treatme t The combined treatment must therefore be preferred

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Table I

Haemodynamic parameters in 12 patients with mild arterial hypertension Average values under placebo diuretic (HOE 118) and combined diuretic + beta-blocker (Baycaron + Inderal)

		Placebo		HOE 118		Baycaron+ Inderal
Body weight	kg					
		73 0	p<0 001	71 3	p<0 001	73 5
Blood pressure	mm Hg					
supine		154/110	- -	140/104	- -	132/95
standing		150/115	- -	139/109	- -	133/99
Heart rate	/minute					
supine		69	p<0 05	72	- -	59
standing		74	- -	84	- -	65
Cardiac output	l/min					
supine		7 3	- -	6 3	n s	6 7
standing		5 7	- -	5 0	n s	4 8
Peripheral vascular resistance	dyn sec cm^{-5}					
supine		1591	n s	1661	n s	1465
standing		1971	n s	2071	n s	2075

placebo (p < 0 001) and furthermore significantly lower under Baycaron + Inderal than under HOE 118 (p < 0 001) Heart rate is the highest under HOE 118 by far the lowest under Baycaron + Inderal Both under HOE 118 and under Baycaron + Inderal the blood pressure

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ACUTE HEMODYNAMIC EFFECTS OF FIVE BETA-ADRENOCEPTOR BLOCKING AGENTS IN MAN. THE SIGNIFICANCE OF SELECTIVITY AND INTRINSIC SYMPATHOMIMETIC ACTIVITY.

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The beta-adrenoceptor blocking agents used in the clinic can be characterized by properties such as selectivity and partial agonism or intrinsic sympathomimetic activity (I s a) In man the physiological significance of these properties is not yet clear, although the importance of selectivity is obvious in the treatment of patients with obstructive lung disease The practical implication of I s a has not been established. Beta-adrenoceptor blockers with and without I s a have been proven to be equally effective in the antihypertensive treatment but any advantage or disadvantage of I s a, has not yet been demonstrated in man.

The present study was undertaken in order to compare the quantitative effects of different beta-adrenoceptor blockers on heart rate cardiac output and arterial blood pressure Dose response curves for the central hemodynamic effects of I v administration of Propranolol non-selective without I s a Atenolol selective without I s a. Pindolol non-selective with I s a Practolol selective with a weaker I s a. and a new beta-adrenoceptor blocker not yet in clinical use ICI 89 406 selective with I s a.

Material and methods.

The study comprised 29 patients (25 men and 4 women) who three to six months earlier have had an acute myocardial infarct The mean age was 54 years ranging from 35 years to 68 years All patients were actively employed None had signs of cardiac failure and none were in diuretic or antihypertensive therapy All patients consented to participate in the study after being informed in details of its nature and purpose

The studies were performed in the morning. The patients having fa ted over night. The patients were in the supine position in a silent room with a constant temperature of 23° celcius Talking was avoided throughout the study and the patients were instructed to keep s immobile s possible but not allowed to fall a sleep The tip of a Swan-Ganz th rmodilution cath ter was placed in the pulmonary a tery under fluroscopic guidance After one hour of supine rest control values for c rdi c output (CO) systemic blood pressure (BP) heart rate (HR) and pulmonary artery pressure (PAP) were obtained in duplicate The CO values used in the following were mean value of five consecutive determinations done within two or three min using an Edvards c rdiac output computer Thereafter with 15 min interv l six doses of one of the beta-adrenoceptor blocking agents was administered i v in equipotent logarithmic incremental doses Twelve to 15 min after each injection the above mentioned variables were recorded. In each group the total cumulative dose after the sixth injection of the respective drugs was Propr nolol 0 18 mg/kg b. w n = 5. At nolol 0 18 mg/kg b w n = 6 Pindolol 0 023 mg/kg b w n = 6 Practolol 0 64 mg/kg b w n = 5 ICI 89 406 mg/kg b w n = 7

Results:

The dos response curves for HR and CO expressed s per cent change from the ontrol values are shown in Fig 1 The curves fall into three groups according the degree of i a.: a) the curves for pindolol and ICI 89 406 which do not diffe significantly from control values b) the urve fo practolol which diff rs significantly from group a as well as group c and c) the urves for propranolol and atenolol It is seen that the l t two drugs caused the most pronounced decrease in HR and CO The BP was essentially unchanged in all patients after the sixth dose Thus the tot l peripher l vascular resistance was unchanged after pindolol and ICI 89 406 moder tely increased aft r practolol and markedly incre sed after prop anolol and atenolol

Th mean PAP was ignificantly increased by three to five mm Hg fter propranolol and atenolol but essentially unchanged after practolol pindolol and ICI 89 406

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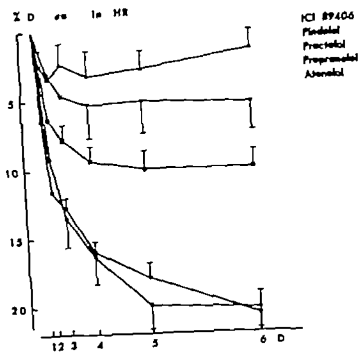
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% Decrease in CO

Pindolol
ICI 89406
Practolol
Propranolol
Atenolol

5
10
15
20
25
30

1 2 3 4 5 6 Dose

Fig 1 Dos response curves f r heart rate (HR) and cardiac output (CO) after i v administr tion of six equipot nt logarithmic incremental doses of five bet adrenoceptor blocking agents to resting man. Mean values ±

Discussion

The present results do not agree with previous results from animal experiments In anaesthetized dogs acute i v administration of practolol up to 4 mg/kg b w had only little effect on the aortic flow Propranolol and atenolol at the same dose level exerted a progressive depressant action with 50 per cent and 30 per cent reduction respectively (2) However the total cumulative doses in the animal experiments were 20 times higher than the doses used in our study i e unrealistically high for clinical use The depressant action of propranolol did not differ from that of atenolol up to a cumulative dose of 0 25 mg/kg i e within the dose range used here Therefore we *find it justified to conclude that the acute hemodynamic effects of* non-selective and selective beta-adrenoceptor blocking agents do not differ significantly from one another within the dose ranges used normally in man

Do these acute results apply also to long-term treatment with beta--adrenoceptor blockers? With respect to the decrease in HR and CO the long-term effects of propranolol and atenolol seem to be identical to the acute effects here found (3 4 5 6 7) For pindolol it is interesting to note that 16 months oral treatment with 34 mg pindolol a day did not change CO neither at rest nor during exercise in the hypertensive patients Although HR was significantly reduced in both situations (1)

Thus we find it justified to conclude that the degree of i s a. possesed by a given beta-adrenoceptor blocking agent is responsible for the acute changes of HR and CO whereas selectivity is of minor if any importance in this respect

PATHOPHYSIOLOGICAL MECHANISMS OF THE ANTIHYPERTENSIVE EFFECT OF A CARDIOSELECTIVE BETA-ADRENOCEPTOR BLOCKING DRUG (METOPROLOL)

Susanne Ljungman Marianne Hartford Mattias Aurell and Göran Berglund
From the Medical Clinic I Sahlgren s Hospital Gothenburg Sweden

Many attempts have been made to identify those hypertensives who could obtain good blood pressure control on beta-adrenoceptor blocking therapy Reduction of blood pressure has been correlated to the initial sympathetic activity and to different cardiovascular and renal physiological variables in several studies Hansson (1973) studied 15 selected men of different ages with essential hypertension He found no correlation between blood pressure reduction on propranolol and variables such as heart rate cardiac output peripheral resistance urinary excretion of catecholamines or plasma renin activity (PRA) Nor did Birkenhäger (1971) or Amery (1976) find that initial PRA or any cardiovascular parameter were s itable predictors of a good blood pressure reduction with propranolol or atenolol

However other workers have found initial PRA to be significantly correl ted to the blood pressure reduction Bühler et al (1973) studied the effect of beta adrenoceptor blocking th rapy on 74 sel cted men and women with essential hypertension Hypertensives with h gh or normal PRA in relation to their sodium excretion had a good blood press re reduction but individuals with low PRA responded poorly These findings were confirmed by Hollifield et al (1976) Karlberg et al (1976) and by von Bahr et al (1976)

Th s th re is uncertainty as to whether factors suitable for gui d nce to the choice of antihypertensive treatment with beta-adrenocepto blocking agents exist The aim of our study was to further analyse the relationship between the antihypertensive effect of the cardioselective beta adrenoceptor blocker metoprolol and factors which are considered to be of importance for maintainance of high

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blood pressure These relations were studied in an unselected epidemiologically defined hypertension population

Material

By blood pressure screening of a random sample of 49-year-old men (n= 3 205) in Gothenburg (participation rate 74%) 74 untreated men with diastolic blood pressure (DBP) over 115 mm Hg were found 6 persons refused further cooperation but 68 men had their blood pressure measured at least three times at the hypertension out patient clinic while participating in a routine clinical work-up The mean of three DBP was ≥ 100 mm Hg in 38 of the 68 men The remaining 30 men had either diastolic blood pressure below 100 mm Hg or had secondary hypertension Of the 38 men with essential hypertension 9 persons were excluded before treatment was started or during the treatment with metoprolol Thus totally 29 patients were treated with metoprolol as the only drug for two months 10 patients belonged to WHO-group I 18 to WHO-group II and one to WHO-group III

Methods

At screening the blood pressure was measured in the seated position without previous rest At the hypertension clinic the blood pressure was measured in the supine position after five minutes rest Prior to treatment the patients were subjected to an investigation of cardiac and renal function Cardiac output was determined by impedance cardiography (Kubicek et al 1970; Granerus et al to be publ) Plasma volume (^{131}I-RIHSA) heart volume (calculated from x-ray ml/m^2 BSA) total peripheral resistance in the leg (calculated from plethysmography and BP) were measured Left ventricular hypertrophy was estimated by orthogonal ECG according to Frank (the height of the R-wave in lead X) and left ventricular distensibility was expressed as the a/H-ratio on the apex cardiogram Sodium excretion (mean of three 24-hour-collections) was determined with the patients on free diet Renal blood flow (PAH-clearance and haematocrite) and renovascular resistance (calculated from renal blood flow and BP) were measured The PRA and p-aldosterone (venous plasma samples after 2 hours supine rest at 9-10 a m) were analysed according to Giese et al (1970) and radioimmunoassay respectively P-noradrenaline was determined by an isotope derivative method (Eriksson et al 1977)

The dose of metoprolol was initially 100 mg b i d and was increas after two weeks to 200 mg b i d if the DBP was above 95 mm Hg The blood pressure was recorded after two four and eight weeks Mean blood pressure (MAP) before treatment (the initial pressure) and after two months treatment were compared MAP was calculated as 1/3 of the pulse pressure + DBP The reduction of the initial pressure after treatment is expressed in per cent of the initial pressure Routine statistical methods were used

Results

Reduction of blood pressure

After two months of metoprolol treatment the blood pressure decrea from 163/106 mm Hg to 142/92 mm Hg The reduction of MAP was 13% 20 patients had a well controlled blood pressure (DBP≤ 95 mm Hg) on 100 mg b i d and so had 4 patients of the 9 who took 200 mg b i d Thus 24 of 29 patients (83%) had an adequate blood pressu control with metoprolol only There was a significant positive correlation between MAP before and MAP after treatment i e the higher the blood pressure was before treatment the higher it was after No significant correlation was found between the initial blood pressure and the blood pressure reduction either the latter was expressed in absolute figures or in per cent of initial value

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Sympathetic activity

Neither p-noradrenaline at rest (r= 0 28) u-noradrenaline during daytime (r= 0 21) nor initial heart rate (r= 0 05) were correlated to the per cent decrease of MAP Presuming that p-noradrenaline and u-noradrenaline measure the sympathetic activity we could not find that persons with a high sympathetic drive had a better response to beta-adrenoceptor blockade than those with a low sympathetic drive

The renin-aldosterone system

A significant positive correlation was found between the blood pressure reduction and the initial PRA (r= 0 69 p< 0 001) Those with a high PRA before treatment had a good blood pressure reduction and vice versa No correlation between p-aldosterone and BP-reduction was found (r= 0 02)

Discussion

These results are the first to be presented from a study of pathophysiological mechanisms in essential hypertension 49-year-old men participated in a blood pressure screening scheme and a subsample underwent extensive investigations of cardiac and renal function 74 untreated persons with a diastolic blood pressure >115 mm Hg were found corresponding to a prevalence of 3 1%

We treated 29 men with metoprolol 200-400 mg daily and observed a significant positive correlation between the per cent reduction of the mean arterial blood pressure and the initial PRA However there was no correlation to any cardiac or renal parameter or to the sympathetic activity In contrast to other similar studies so far published the present one was carried out in hypertensive men homogenous with respect to age and sex Whether the observed statistical correlation between PRA and the antihypertensive effect reflects a causal relation is not known This observation supports the hypothesis that the PRA can be used to predict the antihypertensive effect of beta-adrenoceptor blockade The reason why this relation has been demonstrated in some studies but not in others may well be due to differences in age sex race and earlier antihypertensive treatment of the patients studied

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EFFECTS OF METOPROLOL ON ADRENERGIC MECHANISMS DURING LONG- AND SHORT TERM ANTIHYPERTENSIVE TREATMENT OF SPONTANEOUSLY HYPERTENSIVE RATS

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The antihypertensive effect of β-adrenoceptor antagonists manifests itself in the course of prolonged treatment as a gradual decrease in peripheral resistance In man cardiac output is similarly reduced by acute and prolonged administration whereas mean arterial pressure (BP) is lowered only by long-term treatment as the reflexly increased peripheral resistance is gradually reduced (Tarazi and Dustan 1972) The mechanism underlying the apparent vasodilatation remains to be clarified Among the various mechanisms suggested we have studied the possible interference with the adrenergic vasomotor control in experimental animals

In the spontaneously hypertensive rat (SHR) a single i v dose of metoprolol reduced heart rate without affecting BP whereas repeated administration by the i v or oral route resulted in BP reduction within the first week of administration (Ljung et al 1976) Furthermore long-term administration of propranolol or metoprolol to growing SHR has been shown to prevent the development of hypertension (Weiss et al 1974) Long-term antihypertensive treatment was found to be associated with impaired vasoconstrictor responses to sympathetic nerve stimulation in the isolated portal vein (Ljung et al 1975) and with reduced rate of adrenal catecholamine synthesis (Åblad et al 1977)

The present experiments were designed to elucidate whether any changes in the adrenergic system found after long-term preventive treatment with the β_1-selective antagonist metoprolol could also be observed after short term curative antihypertensive treatment of adult SHR and thus make it possible to distinguish between secondary changes and primary effects

MATERIAL AND METHODS

Female SHR of the Okamoto strain (Møllegaards avlslab A/S) were used A long-term treated group was fed pelleted food containing 3 mg/g from the age of 6 weeks for 6 5 months The short-term treated group received control food during the inital 6 months of the study and then the same diet with metoprolol added for two weeks whereas a control group received the standard diet throughout In the course of the study long-term treated and control rats were housed in metabolic cages for two weeks and urine was collected in acid over 24 h periods during the 2nd week for determination of catecholamines by a radioenzymatic method

Towards the end of the study chronic catheters were implanted into the aorta via the left femoral artery and exteriorized in the neck in every second rat of each group At this time metoprolol administration was discontinued Mean arterial blood pressure and heart rate (HR) were continously monitored in a computer system during three 2 h sessions during the 2nd and 3rd day after surgery values from an individual rat were averaged to give one

respectively The animals were then sacrifi ed and isolated portal vein preparations were mounted in organ baths for studies of vascular neuro-effector function (see Ljung et al 1975) Furthermore hearts ere isolated for determination of left ventricular wet weight and adrenals were frozen after rapid dissection for determination of dopamine (DA) content

Locomotor activity was recorded in rats not subjected to BP measurement The nimals were placed in exptl cages and spontaneous movements were recorded during the initial 10 min period by a photo-electric method

In a separate set of experiments adult female SHR were treated with metoprolol 3 mg/g for 8 weeks The animals were then decapitated and their hearts portal veins superior mesenteric a teries and adrenals were rapidly isolated for determination of endogenous NA content by means of a radioenzymatic method

RESULTS

The results are summarized in table I

Table I

Effects of oral metoprolol (3 mg/g food) treatment of SHR for 6 5 months during development of hypertension (long-term treatment) or during two weeks at adult age (short-term treatment) Mean ± SE

Variable	Control C	Long-term treatment L	Short-term treatment S
Mean arterial blood pressure (mmHg)	181 ± 5 n=6	149 ± 4 n=7	157 ± 5 n=9
Heart rate (bpm)	387 - 8	376 ± 10	394 - 8
Body weight (g)	251 ± 5	226 - 5	235 ± 6
Left vent icular weight (% of BW)	0.33 - 0 01	0 29 ± 0 01 Δ	0.35 ± 0 01
Adrenal DA content (nmoles)	2 68 + 0 52	1 55 ± 0 09	1 78 + 0 18
Urinary NA (nmol/d)	8 57 ± 0 37 n=9	9 52 ± 0 43 n=9	
Urinary DA (nmol/d)	31 5 ± 1.37	33 0 ± 0 90	
Locomotor activity (counts)	179 ± 13.3 n=10	187 11 4 n=11	168 - 13.8 n=8
Portal vein NA $-\log ED_{50}$ (M)	6 11 0 06 n=7	6 11 ± 0 06 n=7	6 06 + 0 07 n=8
Portal v in NS $-\log f_{50}$ (Hz)	0 60 - 0 02	0 58 ± 0 02Δ	0 64 ± 0 02

indicates p < 0 05 as compared to control

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The mean arteri l blood pressure was significantly lowered in both of the treated groups s compared to control whereas no significant difference was found between the pressure levels after long-term and short term treatment respectively Heart rate was the same in all three groups indicating that no significant β-adrenoceptor blocked prevailed at the time of recording The left vent icular weight expressed as a percentage of body weight was lowered after long-term preventive treatment and aft r 8 weeks curative treatment but not after short-term treatment

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In the isolated portal vein preparation there was no apparent difference in the spontaneous myogenic activity nor in the maximum force generated in response to NA The sensitivity to exogenous NA (log ED_{50} value) was not different in the three groups and the responses to transmural nerve stimulation were likewise comparable After α-adrenoceptor blockade isoprenaline readily casued inhibition of the myogenic activity in portal veins from all three groups

The adrenals were analyzed for dopamine (DA) content as an index of sympatho-adrenal discharge (see discussion) The DA levels were markedly reduced in the adrenals of SHR exposed to long-term as well as short-term treatment as compared to control On the other hand the daily urinary output of NA or DA was not different in SHR exposed to long-term treatment For technical reasons catecholamine excretion was not tested in rats subjected to short-term metoprolol treatment Exploratory behavior measured as locomotor activity dyring an initial 10 min period was not interfered with by metoprolol treatment

In SHR treated with metoprolol for 8 weeks the relative cardiac weight was significantly lower (0 39±0 006 % n=7) than in control SHR (0 42±0 015 % n=5) The cardiac NA content was slightly elevated (5 2±0 30 vs 4 4±0 24 nmoles) like in the adrenals (109±3 7 vs 87±2 9 nmoles) and in the portal vein (11 4±1 07 vs 8 9±0 65 nmoles/g) in the treated rats compared to control Although not statistically significant the same tendency of increased NA level was found in the superior mesenteric artery (8 6±0 89 vs 7 7±0 89 nmoles/g)

DISCUSSION

In accordance with earlier studies long-term treatment of SHR with metoprolol during development of hypertension (Weiss et al 1974 Ljung et al 1975) and short-term treatment during established hypertension (Ljung et al 1976) resulted in lowered blood pressure as compared to control As previously discussed (Ljung et al 1976) the antihypertensive effect of metoprolol in SHR resembles that in hypertensive patients with regard to time of onset extent of response and plasma concentrations of metoprolol required

In contrast to previous findings (Ljung et al 1975) however the neurogenic responses of the isolated portal vein were not depressed after long-term treatment This does not necessarily imply a qualitative difference between the effects of metoprolol on the peripheral neuro-effector function in the two studies Acute blockade of the prejunctional β-adrenoceptor mediated positive feed-back mechanism in isolated portal vein of SHR by dl-propranolol causes a reduction in transmitter release per impulse of up to 30 per cent without depression of the effector response (Dahlöf et al 1978) Thus reduced transmitter output may have ...ed during nerve stimulation in the tissues from the treated animals but

the extent of reduction has not been sufficiently large to attenuate responses

The findings of a lowered DA content in the adrenals both after short and long-term metoprolol treatment indicate a reduced rate of catecholamine synthesis which may reflect reduced rate of discharge in the adrenergic system (Carlsson et al 1973) In subsequent experiments (Almgren unpublished) it has been shown that the depression of the rate of adrenal catecholamine synthesis during metoprolol treatment is indeed mediated via nervous mechanisms rather than a direct effect of the agent on the adrenal medulla The slight increase in NA content of the heart the blood vessels and in the adrenals found after 8 weeks metoprolol treatment may support this tenet (cf Carlsson et al 1977) In the rabbit Raine and Chubb (1977) have found biochemical support for and Lewis and Haeusler (1975) electrophysiological evidence of reduced rate of sympathetic nerve discharge during prolonged administration of β-adrenoceptor antagonists It is of interest that the urinary excretion of NA was not lowered in long-term treated SHR Thus the amount of intact NA recovered in the urine may not adequately reflect the sympathetic activity of the animal The rats were not sedated by the metoprolol treatment as apparent from the lack of effect on exploratory behavior This refutes the possibility that BP and sympathetic activity were simply reduced secondary to an ove all decrease in mental or physical activity

In conclusion the present expe iments demonst ate that metoprolol during long-term preventive treatment nd during short-term curative treatment causes reduced BP in the SHR The results point to a primary involvementof the adrenergic cardiovascul r control mechanisms and e conclude that a reduced r te of discharge is one mechanism by which metoprolol exe ts its antihypertensive effect in SHR

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In SHR treated with metoprolol for 8 weeks the relative cardiac weight was significantly lower (0 39±0 006 % n=7) than in control SHR (0 42±0 015 % n=5) The cardiac NA content was slightly elevated (5 2±0 30 vs 4 4±0 24 nmoles) like in the adrenals (109±3 7 vs 87±2 9 nmoles) and in the portal vein (11 4±1 07 vs 8 9±0 65 nmoles/g) in the treated rats compared to control Although not statistically significant the same tendency of increased NA level was found in the superior mesenteric artery (8 6±0 89 vs 7 7±0 89 nmoles/g)

DISCUSSION

In accordance with earlier studies long-term treatment of SHR with metoprolol during development of hypertension (Weiss et al 1974 Ljung et al 1975) and short-term treatment during established hypertension (Ljung et al 1976) resulted in lowered blood pressure as compared to control As previously discussed (Ljung et al 1976) the antihypertensive effect of metoprolol in SHR resembles that in hypertensive patients with regard to time of onset extent of response and plasma concentrations of metoprolol required

In contrast to previous findings (Ljung et al 1975) however the neurogenic responses of the isolated portal vein were not depressed after long-term treatment This does not necessarily imply a qualitative difference between the effects of metoprolol on the peripheral neuro-effector function in the two studies Acute blockade of the prejunctional β-adrenoceptor mediated positive feed-back mechanism in isolated portal vein of SHR by dl-propranolol causes a reduction in transmitter release per impulse of up to 30 per cent without depression of the effector response (Dahlöf et al 1978) Thus reduced transmitter output may have occurred during nerve stimulation in the tissues from the treated animals but

the extent of reduction has not been sufficiently large to attenuate responses

The findings of a lowered DA content in the adrenals both after short and long-term metoprolol treatment indicate a reduced rate of catecholamine synthesis which may reflect reduced rate of discharge in the adrenergic system (Carlsson et al 1973) In subsequent experiments (Almgren unpublished) it has been shown that the depression of the rate of adrenal catecholamine synthesis during metoprolol treatment is indeed mediated via nervous mechanisms rather than a direct effect of the agent on the adrenal medulla The slight increase in NA content of the heart the blood vessels and in the adrenals found after 8 weeks metoprolol treatment may support this tenet (cf Carlsson et al 1977) In the rabbit Raine and Chubb (1977) have found biochemical support for and Lewis and Haeusler (1975) electrophysiological evidence of reduced rate of sympathetic nerve discharge during prolonged administration of β-adrenoceptor antagonists It is of interest that the urinary excretion of NA was not lowered in long-term treated SHR Thus the amount of intact NA ecovered in the urine may not adequately reflect the sympathetic activity of the animal The rats were not sedated by the metoprolol treatment as apparent from the lack of effect on exploratory behavior This refutes the possibility that BP and sympathetic activity were simply educed secondary to an overall decrease in mental o physical activity

I conclusion the present experiments demonstrat that metoprolol during long-t rm preventive treatment and during short-term curative treatment causes reduced BP in the SHR The results point to a primary involvementof the adrenergic cardiovascular control mechanisms and we conclude that a reduced rate of discharge is one mechanism by which metoprolol exerts its antihypertensive ffect in SHR

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BETA ADRENERGIC BLOCKADE AND VASOSPASM

Olav Thulesius

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INTRODUCTION

Vasospastic disorders of the digital circulation such as Raynaud-phenomena are known side-effects of treatment with beta-adrenergic blockade (Marshall et al 1976) To the present time there is no satisfactory explanation of the underlying patho-physiological mechanism We therefore studied the digital circulation in 3 patients with beta blocker-induced Raynaud-phenomena

METHODS

The method employed is based on measurement of critical closing pressure in the digits using strain-gauges applied to the distal phalanx and a small tourniquet encircling the middle phalanx The pressure changes in this cuff were induced by water which at the same time also could be used for local cooling of the digit Changes in finger temperature were elicited by perfusion with water at different temperatures (30-5^{o}C) An additional cuff on the same digit applied to the proximal phalanx was used to arrest the circulation during the cooling procedure Control pressure was recorded in the arm and another finger The method has been introduced by Nielsen et al (1978)

RESULTS

Three patients treated with beta-blockers (propranolol and metoprolol) who developed Raynaud-phenomena were investigated during and 3 weeks after withdrawal of treatment Fractional digital pressure determined with strain-gauge technique upon cooling i shown in table I It can be seen that although systemic blood pressure was unchanged pressure drop in the digital arteries was less pronounced in all three cases In case No 2 critical closing of the digital circulation occurred at 5^{o}C during treatment with metoprolol but after withdrawal this was eliminated

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		Temperature in digit Co						
		35	30	20	10	5	BP	Drug
1	before	0 95	1 05	1 02	0 65	0 50	155/95	Propranolol
	after	1 00	1 00	0 90	0 78	0 75	150/95	
2	before	1 00	1 00	0 94	0 45	0	145/80	Metoprolol
	after	0 90	0 90	0 65	0 31	0 24	150/80	
3	before	1 08	1 05	1 02	0 65	0 50	155/95	Propranolol
	after	1 00	1 00	1 09	0 78	0 90	150/95	

Table I Digital arterial blood pressure during gradual local cooling Digital pressure expressed as fraction of control finger pressure blood pressure in brachial artery

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DISCUSSION

Raynaud-phenomena seem to occur more frequently with beta-blockers as compared to other types of antihypertensive treatment (cf Marshall et al 1976) Beta blockers seem to enhance vascular tone in certain areas and especially cutaneous vessels This is not apparent clinically except in patients prone to develop Raynaud-phenomena presumably due to an increased vasoconstrictor activity of the digital arteries This could be shown in the present study since critical closing pressure in the digits was reversibly affected by various beta-blockers A reasonable explanation may be enhanced neurogenic alpha-adrenergic tone Moreover an increased humoral stimulation by circulating catecholamines is a possible explanation since it has been shown that both non-selective and cardioselective beta-receptor blockade leads to enhanced noradrenaline responses in connection with stress such as physical exercise (Hansson 1976) Elimination of a tonic beta 2 stimulation does not seem to be a reasonable explanation for the development of this circulatory disturbance since it is caused both by selective and non-selective beta-blockers and the prevalence of cold extremities was equal in patients treated with the cardio-selective beta blocker Atenolol and Propranolol (Simpson 1977)

In 50 cases with intermittent claudication we found equal proportions of patients on beta-blockers and other types of antihypertensive treatment Contrary to disturbancies of the cutaneous circulation such as cold extremities and Raynaud-phenomena intermittant claudication does not seem to be specifically related to beta-blockade but rather any blood pressure lowering treatment as such

		Temperature in digit Co						
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1	before	0 95	1 05	1 02	0 65	0 50	155/95	Propranolol
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EFFECT OF BETA BLOCKADE ON LEG BLOOD FLOW AND LACTATE RELEASE IN EXERCISING MAN

Hans Aström and Anders Juhlin Dannfelt

From the Department of Clinical Physiology Huddinge Hospital Karolinska Institute S 414 86 Huddinge Sweden

Adrenergic mechanisms are involved in the regulation of both circulation and metabolism in the extremities Thus beta adreno-receptor blockade with propranolol has been shown to effectively block the vasodilator effect of catecholamines in the forearm at rest (1 7) Less is known about the effect of betablockade on peripheral vessels during exercise but after long term treatment it has been reported both a decrease in leg blood flow (12) and no decrease (3)

Although beta adrenergic mechanisms are involved in both carbo hydrate and lipid metabolism treatment with therapeutic doses of betablocking drugs has been reported to induce only slight metabolic changes Concerning muscle metabolism chronic treatment with alprenolol decreases the lactate release during exercise despite somewhat higher muscle lactate concentrations (3 4) It is not known whether this also applies during acute blockade and could contribute to the muscle fatigue experienced by some patients on betablockers

Material and Methods

Nine healthy male volunteers participated in the study Teflon catheters were inserted percutaneously into the femoral artery and vein of both legs The tips of the catheters were placed 1 2 cm above the inguinal ligament

The subjects were studied at rest in the supine position and during 15 min upright continuous bicycle exercise at a work load corresponding to approximately 50 % of their maximal oxygen capacity After exercise the subjects rested for 45 min whereupon 2 mg propranolol in 10 ml saline was slowly infused during 5 min in the femoral artery of the right leg Ten minutes later the study was repeated exactly as before the blockade To test the blockade adrenaline was given intra venously as a constant infusion (0 1 µg kg $^{-1}$ min $^{-1}$) in five subjects and after 10 min the determinations at rest were done Ten minutes after stopping the adrenaline infusion the subjects performed the second exerci: test

Leg blood flow was determined by constant intra arterial infusion of indocyanine green dye with sampling in the femoral veins (8) Both at rest and during exercise leg blood flow determinations were made in both legs in randomized order

Arterial and femoral venous blood samples were collected simultaneously at timed intervals for oxygen saturation and lactate determinations

Arterial blood pressure was recorded and the resistance over the vascular bed of the leg was calculated as mean femoral artery pressure (mm Hg) divided by leg blood flow (l/min)

Results

Leg blood flow averaged 0 50 ± 0 06 l/min and there was no difference between the right and left leg (Fig 1a) After betablockade leg blood flow remained unchanged in both legs but when adrenaline was given a 100 % increase appeared in the unblocked leg ($p<0\ 05$) Due to the increased flow leg vascular resistance decreased after adrenaline but remained unchanged in the blocked leg The arterial femoral venous oxygen difference did not change significantly in the blocked leg when adrenaline was infused resulting in an unchanged leg oxygen uptake In the unblocked leg however adrenaline gave a small increase in leg oxygen uptake ($p<0\ 05$)

The arterial lactate concentration averaged 0 59 ± 0 11 mmol/l at rest and increased after adrenaline to 0 93 ± 0 13 mmol/l ($p<0\ 01$) The release calculated as the product of leg blood flow and femoral venous arterial difference was 0 06 ± 0 01 mmol/min in the test leg and 0 07 ± 0 01 in the control leg After adrenaline the release was abolished in the betablocked leg ($p<0\ 05$) whereas it increased in the control leg ($p<0\ 05$)(Fig 1b)

Exercise At the two exercise periodes heart rate increased to a mean of 117 ± 3 and was the same before and after betablockade Both systolic and diastolic blood pressure were uninfluenced by the local betablockade The blood flow in the blocked leg was also unchanged compared both with before propranolol injection and with the contra lateral leg which thus also reflects an unchanged leg resistance (Fig 1a)

The arterial lactate concentration was lower during the second

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Discussion

The main finding in the present study is the marked decrease in lactate release from the leg after acute beta adrenoreceptor blockade with a reduction by almost 50 % during exercise No definite explanation for this can be given but it is worth noting that in the cat skeletal muscle a beta adrenergic dilatator response can be evoked during sympathetic stimulation (10) The neurogenic β-dilatation is confined to the small resistance vessels with little influence on total flow Furthermore the latter study shows that the dilator response can be eliminated by propranolol with a reduction of the transcapillary fluid absorption by 50 % and hence a reduction of the available capillary surface This could explain the decrease in lactate release found in the present study as a result of a mass transport mechanism despite an unchanged total leg blood flow

Another possible explanation for the reduced lactate release could however be a reduced glycogenolysis with less production of lactate No measurement of muscle lactate was done in this study but earlier results both after acute propranolol treatment in dogs (11) and chronic treatment with alprenolol (4) have shown an increased glycogenolysis after β-blockade Furthermore in the latter study higher concentrations of muscle lactate were also found after β blockade which thus indicates that the decreased lactate release is not due to less production of lactate but rather to a changed transport of lactate from the muscle cells to the perfusing blood

A third mechanism for the impaired lactate diffusion could be altered recruitment of the muscle fibres which could alter the relationship between metabolism and perfusion in different areas in the muscles In this context it can be mentioned that ethanol given intra venously has been shown to change the glycogen breakdown in different fibres with increased muscle lactate concentrations (9) which supports the concept of this as a possible mechanism also during beta-blockade

The mechanism that regulates the normal increase in blood flow in exercising muscles has been discussed for several years Local changes secondary to the increase in metablic rate are generally believed to produce the increased flow The results from this study with no difference in leg blood flow between the blocked and unblocked leg during submaximal exercise indicate that the vascular β_2 receptors are not involved in the regulation of leg blood flow during a strenuous steady state exercise

exercise test (p<0 05) In the leg blocked with propranolol the release decreased to 44 % of the preblocked value whereas the release in the control leg was unchanged (Fig 1b)

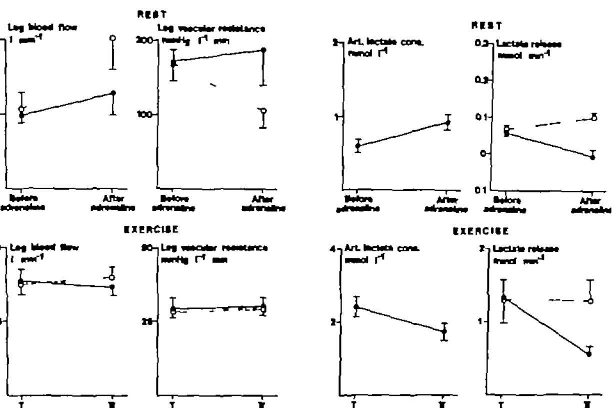


Figure 1

a) Leg blood flow and leg vascular resistance at rest (before and after adrenaline) and during exercise (•——• test leg o -o control leg) Mean ± SEM are indicated

b) Arterial lactate concentration and lactate release at rest (before and after adrenaline) and during exercise (•——• test leg o o control leg) Mean ± SEM are indicated

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Hemodynamic effects of acute and long-term treatment with Labetalol

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Labetal l is a new antihypertensive drug with competitive α and β adrenoceptor-blocking properties (4) The ratio of the α- and β-blocking effects is about 1:3 fter oral administration. Like propranolol labetalol is unselective with respe ts to β_1- and β_2-receptors and it is without intrinsic sympathomimetic activity (9)

It has been suggested that a combination of α- and β adrenoceptor blocking drugs should be ideal for lowering the blood pressure since the l tter should block the eflex effects of the former when the peripheral resistance is lowered by vasodilat tion (5)

The antihypertensive effect have been documented in several studies (2 8)

In contrast with the adrenergic β-blocking agents labetalol can reduce the blood pressure acutely (10)

The purpose of this study was to evaluate the hemodynamic effects of labetalol after acute intravenous administration and after three months oral treatment in patients with essential hypertension.

Material and m thods:

The tudy comprised 10 patients (9 male and 1 female) with essential hypertension (WHO gr de I-II) mean age 48 years range 34 to 61 years All patients consented to participate in the study after being informed in details of its nature and purpose Eight patients were untreated. Two patients had arlier been t eated with diuretics. All the patients had at le st fou weeks placebo period before the fi st hemodynamic evaluation.

The cardiac output (CO) were determined by thermodilution technic using a Swan-Ganz thermodilution catheter nd an Edvards c rdiac output com puter The CO w given as an average of t least five determinations

The blood pressure (BP) was measured sphygmomanometrically The heart at (HR) w regi tered continously by three precordial l ads The tip of

a Swan-Ganz thermodilution catheter was placed in the pulmonary artery under *fluoroscopic guidance* After one hour of supine rest the plasma half-life of indocyanine green (ICG) was determined after an i v bolus injection of 12.5 mg ICG in order to obtain an estimate of the splanchnic-hepatic blood flow Hereafter control values for CO BP and HR were measured in the supine position after five min. of standing and *during the last two min. of supine* bicycle exercise for six min. at 50 watt and 100 watt

After one hours rest labetalol was injected intravenously in a dose of 0 75 mg per kg b w 15 min. later the above described study was repeated using exactly the same protocol

After three month oral treatment with labetalol 1 200 mg orally daily the hemodynamic studies were repeated in five patients as described for the control study

Results:

In the acute study the results are based on ten patients whereas the results in the long-term study at this moment are based on five reexamined patients Both systolic and diastolic BP were reduced significantly after labetalol both in the acute and in the long-term study (see fig. 1)

The *mean values for the mean* BP *(mmHg* $\pm$ 1 SEM) *was* in the control study 138 $\pm$ 2 7 in the supine position 136 $\pm$ 2.8 after five min. standing, 144 $\pm$ 2 0 after six min. of exercise at 50 watt and 152 $\pm$ 2.4 after six min. exercise at 100 watt After acute i v administration of labetalol the corresponding values for mean BP were 119 $\pm$ 2.9 113 $\pm$ 4 6 129 $\pm$ 4 6 and 136 $\pm$ 4 4 respectively After three month oral treatment with labetalol the corresponding values for mean BP were 120 $\pm$ 3 1 116 $\pm$ 4 9 128 $\pm$ 1 7 and 137 $\pm$ 4 8 respectively

Cardiac index was unchanged at rest supine after five min. standing and during six min. of supine exercise at 50 watt as well after acute as after long-term treatment with labetalol

Cardiac index decreased significantly during exercise at 100 watt The mean values (l per min. per m^2) being 7 1 $\pm$ 0 3 in the control study 6 0 $\pm$ 0 2 after i v administration and 6 4 $\pm$ 0 1 after three month oral treatment

There was a *significant decrease* in total peripheral resistance in the supine *and upright* position both after acute and long-term treatment.

During the two exercise periods the *total peripheral resistance* was unchanged after labetalol The HR was unchanged in the supine position after

acute administ ation of labetalol but reduced significantly by 6 per cent fter long term treatment. Both after acute and long term treatment HR was reduced by 5 to 12 per cent after five min. standing and during exercise at 50 watt and 100 watt. The reduction in HR was most pronounced during exercise at 100 watt The stroke index wa significantly increased in the upin position both in the acut and in the long-term study but no significant changes were seen in the upright position and during exercise There was not observed any significant changes in the half life of ICG after labetalol Thi is taken to indicate that splanchnic-hepatic blood flow was unchanged.

Di cussi n

Th significant eduction in BP both after acute and oral administration of labetalol confirm that labetalol is an effective antihypertensive drug. The unchanged cardiac index in the upine position and the eduction during ex rcise in the acute study is in accordance with the results of Koch (6) In the upright position however we have not found any significant changes in cardiac index. Thi contrast to the findings of Koch (6) who found a significant reduction of about 18 per cent in this position. The changes in cardiac index in the long term study are in accordance with the result found by Edvards and Raftery (3) and by Metha and Cohn (7)

The only diff rence between the acute and long-term hemodynamic effects of labetalol found here is the reduction in HR seen only after long-term t eatment. Thi is in accordance with the findings of Koch (6) Other investigators have reported a decrease in HR or 7 beats per min. after i v injection of 50 mg labetalol (10) This discrepancy may be ascribed to differences in the resting sympathetic tone as judged by the pretre tment HR.

The hemodynamic effects of labetalol differs markedly from those of propranolol The most st iking differences are the acute reduction in BP the unchanged cardiac index t re t and during standing and the unchanged splanchni -hepatic blood flow These differences may in all likelyhood be scribed to the α adrenoceptor-blocking properties of labetalol

At re t l betalol reduces the periphe al vascul resi tance both acut ly and aft r thre month or l treatment Thi i taken to indicate that the vasodil tor α drenoceptor-blocking effect i pres nt for a longer period of time

Thu from a hemodynami point of view labetalol is an att active antihypertensive drug.

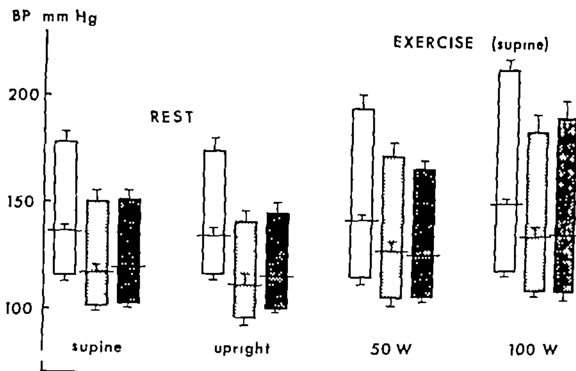


Fig 1 Systolic- mean- and diastolic-blood pressure mean values ± 1 SEM, before open bars after acute labetalol light hatched bars and during long-term oral treatment dark hatched bars

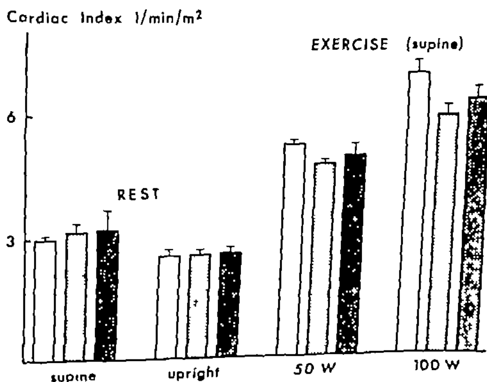


Fig 2 The cardiac index during supine rest when standing and during supine exercise at 50 and 100 watt Symbols as in Fig 1

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HEMODYNAMIC LONG-TERM EFFECTS OF LABETALOL IN ESSENTIAL HYPERTENSION

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INTRODUCTION

From a hemodynamic point of view antihypertensive drugs being able to reduce total peripheral resistance would seem to be of particular interest since this is increased in most patients with established hypertension (6) Labetalol posesses both alpha- and beta-adrenergic blocking properties (1 13) and short term (3 4) and a few long-term (5 2) hemodynamic studies in hypertensive patients have suggested a reduction in total peripheral resistance by this compound

This paper is a short report of the effects of labetalol on central hemodynamics at rest and during exercise in subjects with moderate essential hypertension before and after one year on treatment The full paper including studies of plasma concentrations of labetalol will be published elsewhere (12)

MATERIAL AND METHODS

The study included 15 men mean age 47 5 years with untreated essential hypertension in WHO stage I The hemodynamic study was performed with subjects resting (supine and sitting) and during exercise at 50 100 and 150 Watt Intraarterial blood

pressure was recorded continuously by a catheter in the brachial artery Heart rate was recorded by ECG cardiac output by dye dilution method (Cardiogreen) and oxygen consumption by Douglas bag and micro Scholander method (6)

Labetalol was given as tablets twice daily 200 800 mg/day (mean dose 450 mg/day) Two subjects almost syncopated when sitting in the ergometer chair after the 150 W load at the restudy No other serious side effects were seen

RESULTS

The casual blood pressure dropped in all subjects the mean values from 167/110 to 134/88 mmHg

The major hemodynamic changes are shown in fig 1
The oxygen consumption did not show significant changes
The heart rate decreased significantly at rest (18%) and during exercise (19%) The stroke volume was unchanged at rest sitting but increased significantly at rest supine and during exercise (8%) Thus the cardiac index decreased less than the heart rate at rest supine only 7% (not significant) At rest sitting the decrease was 17% (significant) and during exercise 11% (significant) The intraarterial pressure decreased considerably about 23% at rest and 21% during exercise all changes highly significant Ten of 15 patients became normotensive (BP 140/90 mmHg at rest sitting) The total peripheral resistance decreased in most patients the mean decrease was 19% (significant) at rest supine and 13% (significant) during exercise At rest sitting the decrease was less 11% (not significant)

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MATERIAL AND METHODS

The study included 15 men mean age 47 5 years with untreated essential hypertension in WHO stage I The hemodynamic study was performed with subjects resting (supine and sitting) and during exercise at 50 100 and 150 Watt Intraarterial blood

in similar patients The results resemble those seen after long term therapy with the combination of prazosin and a beta blocker (11) and agree well with what should be expected from a drug with both alpha and beta adrenergic blocking properties The reduction in blood flow is clearly less than what is seen by the use of beta blockers alone and the reduction in total peripheral resistance is significant

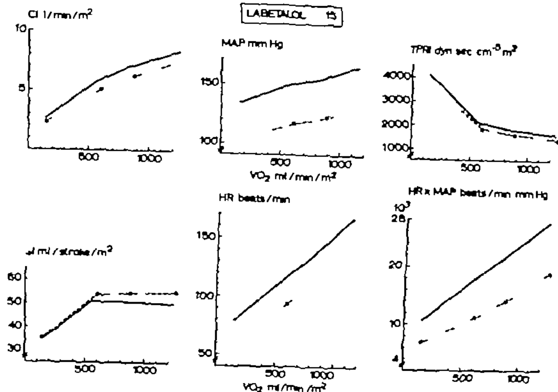


Figure 1 Mean (n=15) hemodynamic changes at rest sitting and during exercise before ——— and during ------ treat ment with labetalol CI = cardiac index MAP = mean arterial pressure TPRI = total peripheral resistance index SI = stroke index HR = heart rate

DISCUSSION

Labetalol was a very effective antihypertensive drug in these patients with moderate essential hypertension The pressure reduction was obtained through a combination of decrease in total peripheral resistance and in cardiac output This hemo dynamic profile differs from what is seen by the use of thiazide diuretics (7) beta-blockers (9 10) or prazosin (8)

LABETALOL IN THE TREATMENT OF SEVERE ESSENTIAL HYPERTENSION: RELATIONSHIP BETWEEN ARTERIAL BLOOD PRESSURE, PLASMA CATECHOLAMINES, PLASMA RENIN ACTIVITY, PLASMA ALDOSTERONE AND BODY WEIGHT.

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INTRODUCTION

In the majority of patients with essential hypertension the sympathetic nervous activity is normal (7 8) and recently it has been *suggested* that the renin system activity declines with progression of essential hypertension except in the malignant phase (12) During antihypertensive therapy however blood *pressure* (BP) regulation may be influenced by alterations in the activities of the sympathetic nervous system and the renin system (1 3 10)

In the *present* study the interrelationships between BP the sympathetic nervous activity the renin-aldosterone system and sodium and fluid balance - as judged by alterations in body weight (BW) - were assessed in patients with severe essential hypertension during combined alpha- and beta-adrenergic receptor blockade induced by oral labetalol treatment

MATERIAL AND METHODS

Twelve patients with severe essential hypertension (WHO stage 2-3) 10 males and 2 females aged 32-67 years were included in the study Before the study 8 patients had received oral diazoxide therapy during several months and the remaining 4 were candidates for oral diazoxide therapy because of resistance to conventional antihypertensive treatment

All antihypertensive agents except furosemide were gradually discontinued during several weeks before the study while the patients were controlled in the out-patient clinic Furosemide in a dosage of 80-250 mg/d was then continued throughout the study period in the same dosage in each patient After treatment with furosemide as the only drug for 2 weeks labetalol was given in increasing dosages *from* 300 to 1200-2400 mg/d divided in 3 daily ...

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not changed further after treatment for 2 months PA and blood glucose concentration did not change significantly during treatment with labetalol

Renin-aldosterone system

Before treatment with labetalol PRA and PAC values were normal or slightly elevated probably due to furosemide treatment No differences in pretreatment values of PRA and PAC were present between patients in whom BP did not respond to labetalol alone and those in whom BP responded to labetalol The changes in PRA and PAC during treatment with labetalol varied greatly Thus PRA decreased by 19-53% in 6 increased by 51-118% in 4 and remained unchanged in 2 patients and PAC decreased by 34-47% in 5 increased by 91-192% in 3 and remained unchanged in 4 patients The changes in mean values of PRA and PAC during treatment with labetalol were not significant Labetalol induced a slight but significant increase in plasma potassium concentration from 3 3 to 3 6 mEq/l ($p < 0\ 05$)

Relationship between the variables studied

No correlation was found between the basal values of the variables in study Changes (Δ) in the variables after 2 months of treatment with labetalol however disclosed some significant correlations Thus ΔBW correlated closely and inversely to ΔPMA (rho=-0 82 $p < 0\ 01$) and to ΔPRA (rho=-0 75 $p < 0\ 01$) Also Δmean BP correlated inversely to ΔPRA (rho=-0 63 $p < 0\ 05$) and to ΔPAC (rho=-0 61 $p < 0\ 05$) Furthermore ΔPRA correlated positively to ΔPMA (rho=0 82 $p < 0\ 01$) and to ΔPAC (rho=0 66 $p < 0\ 05$) Finally a negative correlation between Δmean BP and ΔPMA (rho=-0 58 $0\ 10 > p > 0\ 05$) and a positive correlation between Δmean BP and ΔBW (rho=0 50 $p > 0\ 10$) were at a borderline level of significance

DISCUSSION

The present study indicates that combined alpha- and beta-adrenergic receptor blockade induced by labetalol may provide an adequate control of BP in patients with severe essential hypertension

Contrasting to the expected increase in PMA during an alpha- and beta adrenergic receptor blockade (3) labetalol in the present study induced a decrease in PMA This might however be caused by interference of the sympathetic nervous activity by sodium and fluid retention indicated to occur by a significant in-

month and this treatment was continued unchanged during the second month In 5 patients BP was not reduced and labetalol was supplemented with hydralazine 75-200 mg/d divided in 3 daily dosages during the third month

Blood samples for measurements of plasma noradrenaline concentration (PNA) plasma adrenaline concentration (PA) plasma renin activity (PRA) and plama aldosterone concentration (PAC) were collected by an indwelling peripheral venous catheter at 9 00 a m after recumbence for one hour and an 8-hour fast just before start of treatment with labetalol and every month during the next 2 or 3 months No dietary restrictions were prescribed Plasma catecholamines were determined by a sensitive double-isotope derivative technique (2) PRA was measured as described by Giese & al (5) and PAC was measured according to the method of Damkjær Nielsen (11) BP measured by sphygmomanometry and pulse rate were determined after one hour in the supine position and after 2 minutes in the upright position In association with the BP readings BW was measured

RESULTS

The results are summarized in table I

Blood pressure and pulse rate

Labetalol and furosemide - in 5 patients supplemented with hydralazine - reduced average supine BP from 214/140 to 173/112 mmHg and average upright BP from 208/139 to 152/105 mmHg ($p < 0\ 01$) The decreases in average supine and average upright pulse rate during treatment with labetalol were significant ($p < 0\ 01$)

Body weight

The increase in mean BW from 77 9 to 80 3 kg during treatment with labetalol was significant ($p < 0\ 01$)

Plasma catecholamines

Before treatment with labetalol values of PNA and PA were normal or slightly elevated probably due to furosemide treatment No differences in pretreatment values of PNA or PA were present between patients in whom BP was unresponsive to labetalol and those in whom BP responded to labetalol Labetalol induced a significant fall in the mean value of PNA from 0 30 to [illegible] treatment for one month ($p < 0\ 05$) which was

Table . Mean values (±SEM) of supine and upright BP (mmHg), supine and upright pulse rate (per minute) BW (kg), PRA (ng/ml/h) [illegible] (ng/ml), PGE (ng Ang I/[illegible] ml/h), AC (ng/100 ml), plasma potassium concentration, (mmol/l) and blood glucose concentration (mg/100 ml) before (A) and during treatment with labetalol for one month (B), for 2 months (C) and for 3 months including patient's on additional hydralazine (D).

Supine BP	114/1	±6/4	2/110	±4/2	1/11	±8/4	71/113	±6/3
Upright BP	190/119	±4/4	44/1	/3	18/110	±9/5	92/105	±9/3
Supine pulse rate				±	78		73	
Upright pulse rate	84		77		74	±	77	
BW	77	±4	74	±4	79	±4	84	±
PRA		30±0.05		31±0		30±0		29±0 04[a]
PA		05±0 01		09±0		.07±0.03		11±0
PGE		70±0 25		37±0 35		1.74±0 41		60±0 13[a]
PAC	30	1.		±	31	± .8	1.	±1.
Plasma potassium		±0		±0-		±0		
Blood glucose	95				81	±		

a values only from patients on labetalol and hydralazine

crease in mean BW during treatment with labetalol Thus ΔBW correlated inversely with ΔPNA which suggests that PNA decreased in those patients with sodium and fluid retention contrasting to those without sodium and fluid retention in accordance with an inverse relationship between sympathetic nervous activity and sodium

Also sodium and fluid retention might have modified renin release during treatment with labetalol This was indicated by a negative correlation between ΔBW and ΔPRA which suggests that renin release was suppressed in those patients with sodium and fluid retention contrasting to those without retention of sodium and fluid in accordance with the wellknown inverse relationship between renin and sodium A pronounced increase in PRA occurred in some of our patients during treatment with labetalol despite the presence of a beta-adrenergic receptor blockade which usually suppresses renin release (1 6 9) According to the baroreceptor-theory (4) a decrease in BP might have contributed to the stimulatory effect on renin release in these patients supported by the findings of a negative correlation between Δmean BP and ΔPRA

The positive correlation between ΔPNA and ΔPRA found in the present study was probably due to a common action of alteration in sodium and fluid balance upon renin and catecholamine release since the renal sympathetic innervation conceivably was blocked by labetalol

Lack of a correlation between ΔPAC and ΔBW suggests that other hitherto unidentified mechanisms than hyperaldosteronism are involved in sodium and fluid retention associated with labetalol treatment

In conclusion the present study suggests that labetalol through its combined alpha- and beta-adrenoreceptor-blocking action induces important alterations in the state of sodium and fluid balance which affect renin as well as sympathetic nervous activity whereby the antihypertensive effect of labetalol may be modified Further investigations by direct measurements of body sodium and fluid content in stead of BW are necessary to verify such a hypothesis

Table   Mean values (+SEM) of supine and upright BP (mmHg), supine and upright pulse rate (per minute), BW (kg), PRA (ng/ml), PA (ng/ml), PRA (ng AngI/100 ml/h), AC (ug/100 ml), plasma potassium concentration (mEq/l) and blood glucose concentration (mg/100 ml) before (A) and during treatment with labetalol for one month (B), for 3 months (C) and for 3 months inclusive patients on additional hydralazine (D).

Supine BP	214/144 ±8/4	192/138 ±8/7	1/1 ± /8	1/11 ±6/7
Upright BP	208/139 ±6/4	60/1 /5	88/1 ± /8	52/105 ±9/3
Supine pulse rate	83	89 ±	78	72
Upright pulse rate	80	77 ±1	78 ±	77 ±
BW	77 ±1	79 ±4	79 ±4	80 ±4
PRA	30±0 05	.31±0	20±0	.29±0.04[a]
PA	05±0 01	00±0	07±0 01	±0
PRA	78±0 28	37±0 25	1.74±0	80±0.19[a]
PAC	29 ±	±	21 ± .8	±
Plasma potassium	±0	+0	1. +0.2	
Blood glucose	68		±	

a) values only with patients on labetalol and hydralazine

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Table [illegible] Mean values (±SEM) of supine and upright BP [illegible] supine and upright pulse rate (per minute) BW (kg) PRA [illegible] PA [illegible] PRA [illegible] PAC [illegible] plasma potassium concentration, [illegible] and blood glucose concentration [illegible] before (A) and during treatment with labetalol: for one month (B), for [illegible] months (C) and for [illegible] months [illegible] patients on additional hydralazine (D).

	A	B	C	D
Supine BP	[illegible] ±[illegible]	[illegible] ±[illegible]	[illegible] ±[illegible]	[illegible]
Upright BP	[illegible] ±[illegible]	[illegible]	[illegible] ±[illegible]	[illegible]
Supine pulse rate	[illegible] ±	±	[illegible]	[illegible]
Upright pulse rate	[illegible] ±	77		77
BW	77 ±[illegible]	[illegible] ±[illegible]	[illegible]	[illegible] ±[illegible]
PRA	[illegible]	[illegible]	[illegible]	[illegible] [a]
PA	[illegible]	[illegible]	[illegible]	[illegible] [a]
PRA	[illegible]	[illegible]	[illegible]	[illegible] [a]
PAC	[illegible]	[illegible]	[illegible]	[illegible] [a]
Plasma potassium	±[illegible]	±[illegible]	±[illegible]	
Blood glucose	[illegible]	11	[illegible]	

[a] values only from patients on labetalol and hydralazine.

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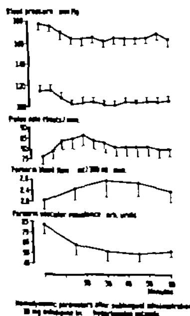
EFFECTS OF NIFEDIPINE ON BLOOD PRESSURE, REGIONAL HEMODYNAMICS, PLASMA RENIN ACTIVITY AND PLASMA CATECHOLAMINES IN PATIENTS WITH ARTERIAL HYPERTENSION.

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The calcium antagonists nifedipine (Adalat[R] BAY a 1040) and verapamil (Isoptin[R]), which were introduced for the treatment of angina pectoris both have a marked effect on the excitation--contraction coupling in vascular smooth muscle (Grün & Fleckenstein 1972) The relaxant effects of these drugs in isolated human vessels have been demonstrated (Mikkelsen et al 1978 a 1978 b) Previous clinical investigations of verapamil as a vasodilator in man indicated that calcium antagonists might be usefull in the treatment of arterial hypertension (Lederballe Pedersen 1978) This necessitated a pilot study of nifedipine as an antihypertensive agent

Eleven patients with essential hypertension of varying severity received a test dose of 10 mg nifedipine by the sublingual route The figure below illustrates the effects on blood pressure heart rate forearm blood flow and calculated forearm vascular resi tance



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In contrast to previous experiences with other potent vasodilators a significant fall in body weight was found Plasma renin activity showed an insignificant increase from 1 2o ± o 27 to 1 8o ± o 54 ng/8o% ml/h after 6 weeks of therapy Side effects in the form of heat sensations in face and limbs was noted in several patients during the first days of treatment Although the side effects tended to vanish after some days they limited the daily dosage in a few of the patients

The results of the present study of nifedipine as an anti-hypertensive agent leaves us with the picture of a powerfull vasodilator with a prompt effect on blood pressure An increase in sympathetic activity manifested by rise in pulse rate plasma noradrenaline and plasma renin activity was found and in consequence of this combined therapy with a betablocking agent might be beneficial Studies of this aspect are in progress

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A significant drop in blood pressure and a concomitant rise in pulse rate occurred already after lo minutes Forearm blood flow rose to maximal values after 3o minutes whereas the calculated vascular resistance reached nadir levels 45 minutes after the administration of nifedipine The decrease in blood pressure lasted for several hours

Plasma concentrations of nifedipine were determined by a fluorometric method(+) A few patients had peak concentrations of nearly 2oo ng/ml after only 15-3o minutes but most patients show a slower absorption with maximum values of about 5o ng/ml after 9o minutes There was a close correlation between the plasma concentrations of nifedipine and the decrease in calculated vascular resistance (at t = 45 min: r = o 86 p < o o2 n = 7) The obtained decrease in blood pressure was not significantly correlated to the plasma concentration of nifedipine

After the acute administration of lo-2o mg of nifedipine there was a rapid rise in plasma renin activity from a mean of 1 4o ± o 33 ng/8o% ml/h at t = o min to 2 lo ± o 51 at t = 6o min (p < o oo5 n = lo) Plasma noradrenaline also showed a rise from o 25 ± o o3 to o 47 ± o o5 ng/ml (p < o ol n = 6) whereas no change was observed in the adrenaline values The increase in plasma renin activity significantly correlated with the basal values (r = o 94 p < o ool n = lo) No significant correlation was present between the increase in plasma renin activity and the rise in plasma noradrenaline

The effects of continued oral treatment with nifedipine was evaluated in a group of lo hypertensive patients who received 3o-6o mg daily for 6 weeks Resting supine blood pressure was reduced from a mean value of 175/115 ± 6/2 to 151/96 ± 4/3 mm Hg (p < o ool) Mean pulse rate increased from 82 ± 2 to 91 ± 4 beats/min (p < o o2) Forearm blood flow was not significantly higher at the end of therapy than before but the calculated forearm vascular resistance showed a significant decrease during therapy

(+) Plasma determinations of nifedipine were kindly carried out by dr Rämsch Bayer AG Leverkusen Germany

(3 women) participated They were informed of the aim of the study and gave their written consent After investigation at the Hypertension Clinic they were classified as having an essential hypertension corresponding to WHO stage I-II The blood pressure was expressed as mean arterial pressure [6] It was based on 3 separate ambulant pressure recordings the group mean value was 117±5 mm Hg The mean age was 46±5 years 20% of the patients belonged to the low renin group according to their fasting plasma renin activity/24 hr urine sodium excretion index The investigation was performed with the patients supine An intravenous cannula was inserted in both forearms one for injection and one for sampling Clonidine was given as bolus injections in doses from 75 to 275 μg 9 patients received 2 doses at separate occasions Heart frequency and blood pressure was measured non-invasively by the same person with a mercury sphygmomanometer every 15 min the hr before the injection and according to a predetermined protocol during 24 hrs after the injection as described [3] Venous sample for clonidine determinations were drawn in connection with the pressure recordings Concentration time data for each subject were then treated with a digital computer program (NONLIN) to find the best fit of a polyexponential equation All value were weighted and given as mean ± S D as described [5]

SHR experiments Blood pressure was registered from an catheter in the a carotis on awake SHR Through an indwelling catheter in v jugularis clonidine was infused at different rates to achieve steady state plasma concentration between 0 5-10 ng/ml as described [4] 5-6 rats were studied at each

RELATIONSHIP BETWEEN CLONIDINE KINETICS AND ITS BLOOD PRESSURE EFFECTS

Marianne Frisk-Holmberg

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Clonidine in daily doses from 0 075-1 2 mg is used in Scandinavia for the treatment of essential hypertension Higher doses are used elsewhere and during chronic administration with approximately 5 4 mg daily giving peak plasma concentrations ∿20 ng/ml the therapeutic response was abolished[7] Davies et al [1] studying healthy volunteers have also reported that the blood pressure lowering effect is reduced when higher plasma concentrations of clonidine are present After bolus doses of 0 15-0 3 mg a hypertensive response has been observed in man[5] Higher doses give a more pronounced blood pressure increase These studies indicate a concentration dependence of clonidine s blood pressure effects The aim of the present investigation was to study relationship between clonidine kinetics and the therapeutic response in essential hypertensives after bolus injections To study the concentration dependence of the blood pressure effects during steady state conditions the spontaneous hypertensive rat (SHR) was investigated

PATIENTS AND METHODS

13 previously untreated healthy patients of both sexes

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between the patients plasma renin status and the blood pressure effect The blood pressure reduction was also significantly correlated to the logarithm of the plasma concentration of clonidine (r=0 86 p 0 01) Concentrations above 0 2 ng/ml gave a significant blood pressure decrease After doses of 0 2-0 275 mg the blood pressure reduction was still present at the 24 hrs observation A positive correlation was also found between clonidine plasma concentrations and the blood pressure reduction all observation points starting after the distribution phase (Fig 1) when an apparent pseudoequilibrium is achieved (r=0 89 p 0 02)

Relationship clonidine steady state concentrations (C_{pss}) and blood pressure effects (SHR)

C_{ps} concentrations of 0 5 ng/ml gave a significant reduction of mean arterial blood pressure 5±2 mm Hg (p<0 05; n=5) The blood pressure reduction was lineary related to the $C_{p\ s}$ of clonidine up to levels of 2 0 ng/ml Above that level the blood pressure reducing effect of clonidine was attenuated and at levels of 8 0 and 10 ng/ml a blood pres ure increase was seen These animal data indicate that clonidine has a narrow plasma concentration range for its blood pre sure reducing effect

DISCUSSION

The present data show that after i v bolus of clonidine there is a significant correlation between the therapeutic effect and the plasma concentration of clonidine at all observation points when an apparent pseudoequilibrium of the drug i achieved The pharmacokinetics of clonidine show that

steady state level Venous sampling for clonidine analysis were drawn Values are mean ± S D

Clonidine was determined in plasma with a gas liquid chromatografic method using an electron-capture detector [2]

RESULTS

Clonidine kinetics After bolus i v doses (0 075-0 275 mg) the plasma concentration time curves displayed a biexponential decay during 0-1440 min The kinetics of clonidine was described by an open 2-compartment model The half-life for the α-phase varied between 2 4-15 1 min and for the β-phase between 7 4-11 4 hrs No significant difference between the half-lives after the different doses was found but the decay of both the α-phase and the β-phase was decreased after the highest dose (0 275 mg) The apparent volume of the distribution (VDβ) was 3 29 l/kg and unaffected by dose A gradual increase in the area under the plasma concentration curve was observed between the 0 075-0 2 mg (256 22±44 min/ml) and the highest dose 0 275 mg (386 min/ml) The mean plasma clearance was 4 ml/min/kg (0 075-0 2 mg) and was lower after the 0 275 mg dose (2 98 ml/min/kg)

Relationship clonidine kinetics and therapeutic response

Clonidine gave a dose-dependent blood pressure reduction The blood pressure decrease was significantly correlated to the logarithm of the dose (r=0 975 p<0 001) from the 0 075 mg dose to 0 275 mg The dose-response curve was steep The mean arterial blood pressure reduction was 38±5 29 mm Hg after the highest dose The heart rate was also reduced but the ... related No relationship was found

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the volume of distribution is high and the mean plasma clearance is 4 ml/min/kg The half-life of the terminal plasma concentration curve between 7-11 hrs and after single doses of 0 10 mg or more blood pressure lowering plasma concentrations of clonidine are still present 12 hrs after the administration This fact would allow a 2 dose regimen

During steady state conditions in the SHR clonidine has a narrow plasma concentration range for its blood pressure lowering effect indicating a therapeutic window This observation could be one explanation for the therapeutic variability and inefficiency of the drug in the clinical situation

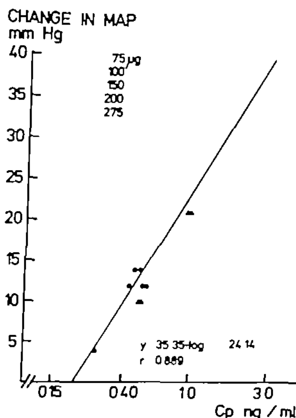


Figure legend

Relationship between reduction of mean blood pressure (MAP) mean value of individual values and mean plasma clonidine
... doses of 0 075-0 275 mg (log scale)

During the first four weeks of active therapy the doses of metoprolol alprenolol and oxprenolol were 100 mg b i d 200 mg b i d and 80 mg b i d respectively During the following eight weeks all patients received respective β-blocker in the double dose These doses of the three β-blockers were regarded as equipotent with regard to reduction of exercise induced tachycardia and are the doses generally recommended in the treatment of hypertension (2) After this dose-finding period the patients were followed up for another 38 weeks with control visits after 12 and 26 weeks respectively During this follow-up period the patients were maintained on the lowest dose giving normotension i e a blood pressure <160/95 mm Hg Patients not satisfactorily controlled on the highest dose were given hydrochlorothiazide 12 5 mg b i d in addition At each control visit systolic and diastolic blood pressure and heart rate were recorded in the sitting position after 5 minutes rest

Unwanted effects were recorded according to a check-list

The following laboratory investigations were carried out after 6 weeks on placebo and subsequently after 12 and 50 weeks on active therapy serum creatinine bilirubin alkaline phosphatase S GOT S-GPT chole terol triglycerides uric acid and A N F

Results

Of the 106 patients who entered the study 91 completed the fi st 3 months on active therapy and 71 patients completed the whole study Only two of the 35 drop-outs were withdrawn due to possible ide-effects of treatment with β-blockers (see under heading Side-effects)

A comparison between metoprolol, alprenolol and oxprenolol in the treatment of hypertension

- A double-blind study over 12 months -

- By Jaakko Tuomilehto -
North Karelia Project
University of Kuopio
Finland

Introduction:

Metoprolol is a β_1-selective β-blocker devoid of intrinsic stimulating activity (I S A) and alprenolol and oxprenolol are two non-selective β-blockers with I S A (1) With the background of these pharmacological differences we undertook the following comparative study between the three β-blockers in order to evaluate their antihypertensive effect and tolerability

Patients and methods

106 patients with a newly discovered and previously untreated hypertension were included into the study There were 94 males and 12 females with a mean age of 42 years range 16 - 68 years All patients belonged to WHO-stage I or II Patients with AV-block chronic obstructive lung diseases cardiac decompensation and insulin treated diabetes mellitus were primarily excluded from this investigation

The design of the study is given in figure 1

After the initial six weeks run-in period on placebo patients with a sitting BP ≥160/96 mm Hg were randomly allocated to one of three parallel groups to be treated with either metoprolol alprenolol or oxprenolol

Compared to placebo all these reductions of the heart rate were statistically significant No significant differences were found between the three β blocker with regard to the reduction of the heart rate

B) Follow-up period

In the subsequent long-term follow-up period up to 12 months the patients were maintained on the lowest effective dose-level of each β-blocker and if necessary hydrochlorothiazide 12 5 mg b i d was added When comparing the three groups with regard to heart rate and blood pressure after this period no differences were found The three groups differed however with regard to dose-level of respective β-blocker and also with regard to the numb r of patients requiring addition of hydrochlorothiazide (HCT)

Of the 20 patients in the metoprolol group 5 were atisfactorily controlled on 200 mg daily 14 on 400 mg daily and only 1 patient needed HCT in addition Of the 25 patients in the alprenolol group 2 patients were satisfactorily controlled on 400 mg daily 15 on 800 mg daily and 8 patients needed HCT in addition In addition one patient in thi group was w thdrawn from the tudy due to poor blood pressure control on alprenolol 800 mg daily Of the 26 patients in the oxprenolol group 2 patients were sati factorily controlled on 160 mg daily 10 on 320 mg daily and the remaining 14 patient required HCT in addition

1 Effects on blood pressure and heart rate (Table I)

A) Dose-finding period

The average blood pressure at the end of the run-in period on placebo was 162/104 164/102 and 163/104 mm Hg in the metoprolol alprenolol and oxprenolol groups respectively

After 4 weeks on the lower dose-level the reduction amounted to 18/10 18/5 and 13/6 mm Hg compared to placebo after metoprolol alprenolol and oxprenolol respectively These reductions of the blood pressure were statistically significant compared to placebo for all three β-blockers After additional 8 weeks on the higher dose-level the corresponding reductions were 23/14 22/8 and 16/8 mm compared to placebo

When comparing the three β-blockers no differences were found with regard to blood pressure on the lower dose-level However on the higher dose-level metoprolol caused a significantly more pronounced reduction of the diastolic blood pressure than alprenolol ($p < 0\ 05$) and oxprenolol ($p < 0\ 05$)

The heart rate on placebo was 75 79 and 78 beats/min in the metoprolol alprenolol and oxprenolol groups respectively After 4 weeks on the lower dose-level the reduction amounted to 7 6 and 8 beats/min and after 12 weeks on the higher dose-level to 14 12 and 10 beats/min on metoprolol alprenolol and oxprenolol respectively

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Metoprolol monotherapy gave a satisfactory blood pressure control in 95% of the patients The corresponding effect was achieved in 68% and 46% of the patients in the alprenolol and oxprenolol groups respectively

2 Side-effects

The frequency of side-effects was low on all three β-blockers A slight increase was seen on the higher dose-level compared to the lower dose-level One patient was withdrawn during treatment with metoprolol due to insomnia in connection with high alcohol consumption and another during alprenolol treatment due to dizziness and tiredness

3 Laboratory investigations after 12 months compared to placebo

The three β-blockers did not cause any significant changes of serum creatinine triglycerides and A N F A minor but statistically significant reduction of serum cholesterol was seen in the metoprolol and oxprenolol groups which might be due to dietary advice Serum bilirubin increased after treatment in each group being significant for metoprolol and oxprenolol Serum uric acid was significantly increased in the alprenolol and oxprenolol groups where addition of HCT was more common than in the metoprolol group No clinical symptoms associated with these changes were found

Conclusion:

In view of the findings in this study metoprolol appears to be more effective than alprenolol and oxprenolol in reducing the diastolic blood pressure when compared in doses regarded as

equipotent with regard to β_1-blockade The number of patients requiring addition of other antihypertensive agents were also fewer on metoprolol than on alprenolol and oxprenolol Another non selective β-blocker pindolol which has a high I S A has also been found to be a less potent anti-hypertensive agent than metoprolol (3) No differences were found between the β-blockers with regard to tolerability during this long-term study ranging over one year

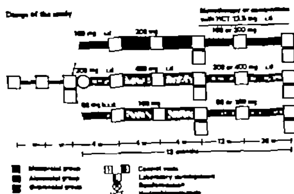


Table [illegible]

	[illegible]	[illegible]	High dose	[illegible]
[illegible]				
Metoprolol	1/104	8/1	1/1	13/1
Alprenolol	104/102	8/5	11/8 [illegible]	16/10
Oxprenolol	1/104	11/6	/8 (n.s.)	13/1
[illegible]				
Metoprolol	75			19
Alprenolol	79		13	
Oxprenolol	78			19

n.s. not significant compared to metoprolol

[illegible] compared to metoprolol

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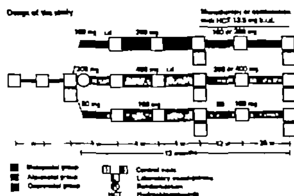


Table Reduction of blood pressure and heart rate compared to placebo Base values

	Isoeba	Low dose	High dose	Monotherapy or combination with HCT
Blood pressure (mm Hg)				
Metopro	162/104	18/1	23/1	3/14
Alprenolo	64/102	18/5	21/8 (n.s.)	26/13
Oxprenolo	[illegible]/ 94	13/6	16/9 (n.s.)	21/14
Heart rate (beats/min)				
Metoprolol	75			18
Alprenolol	79		13	18
Oxprenolol	78			18

n.s. not significant compared to metoprolol
<5 % compared to metoprolol

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HISTAMINERGIC AND RELATED MECHANISMS IN THE CENTRAL CONTROL OF BLOOD PRESSURE

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Histamine is a putative neurotransmitter in the brain (16) The presence of histamine receptors of both the H_1 and H_2-classes in the brain has been demonstrated (2) but their physiological significance is not clear

It has been shown that the antihypertensive drug clonidine (2-[2,6-dichlorophenyl-amino]-2-imidazoline hydrochloride) is able to stimulate histamine H_2-receptors both in peripheral tissues (5 11 16) and in the brain (1 9 10 12, 15) The administration of the specific histamine H -receptor antagonists metiamide (6 9 10 12) or cimetidine (6) intracerebroventricularly antagonises the hypotensive effect of clonidine in urethane-anaesthetised rats. This suggests that cerebral histamine H_2-receptors may mediate the hypotensive effect of clonidine Moreover metiamide alone raises the blood pressure (9) This finding implies that central histamine H_2-receptors are tonically activated in the anaesthetised rat and contribute toward lowering of the blood pressure (9)

The theory of the role of central histamine H -receptors in the control of blood pressure and in the mediation of the hypotensive effect of clonidine is based on studies which indicate that metiamide is a very specific blocker of the histamine H -receptors (3 4) No other significant pharmacological effect of metiamide has been demonstrated for the present. Since the central hypotensive effect of clonidine has been attributed to stimulation of central sympatho-inhibitory α-adrenoceptors (21) the ability of metiamide to block such receptors was studied. The role of histaminergic or related mechanisms in the central control of blood pressure was studied further by using known histamine receptor agonists and antagonists as well as the histamine-related agent imidazole acetic acid.

MATERIALS AND METHODS

Male Sprague-Dawley rats (250–300 g) were anaesthetised with urethane (1.5 g/kg intraperitoneally) The trachea was cannulated with a polyethylene tube and the rats were allowed to breathe spontaneously The mean blood pressure was measured directly from the left femoral artery by means of a pressure transducer The rats were placed in stereotaxic instrument and an injection needle introduced into the lateral cerebral ventricle A polyethylene catheter filled with the solution to be infused was attached to the needle The required amount of solution was allowed to flow slowly by means of hydrostatic pressure. At the end of each experiment, methylene blue was injected and the proper position of the needle in the cerebral ventricle was ascertained.

The following drugs were used Histamine diphosphate (Koch-Light Laboratories Ltd) diphenhydramine hydrochloride (Parke-Davis & Co.) imidazole acetic acid (Sigma Chemical Company) Metiamide and dimaprit were kindly supplied by Dr D.A.A. Owen of Smith Kline and French Laboratories Ltd α-Methylnoradrenaline was donated by Sterling-Winthrop. The doses of the drugs refer to the salt.

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RESULTS AND DISCUSSION

The administration of histamine the natural activator of both H_1-and H_2-receptors into the lateral cerebral ventricle (i.c.v.) induced a dose related rise in blood pressure (Fig 1) The histamine H_1-receptor blocking drug diphenhydramine (100 or 200 μg i.c.v) antagonised the hypertensive effect of centrally administered histamine (Fig. 1) This confirms the earlier report that the central hypertensive effect of histamine is due to the stimulation of histamine H_1 receptors (7)

The possible existence of sympatho-inhibitory histamine H_2-receptors was studied by using the selective histamine H_2-receptor agonist dimaprit (13) The administration of dimaprit i c.v at the doses of 5–80 μg per rat elevated the blood pressure in a dose-related manner At the dose of 80 μg the rise in blood pressure was 21 mm Hg in comparison with the saline treated control group ($p < 0.01$) However this effect of dimaprit was not antagonised by metiamide pretreatment (1 1 mg i.c.v) This finding suggests that the hypertensive effect of dimaprit may be due to some other property of the drug than the stimulation of histamine H_2-receptors. It has been shown that dimaprit is an inhibitor of the histamine catabolising enzymes (17) Further studies are needed to elucidate the mechanism of the central hypertensive effect of dimaprit

The central hypertensive effect of metiamide (9) and the antagonism of the clonidine-

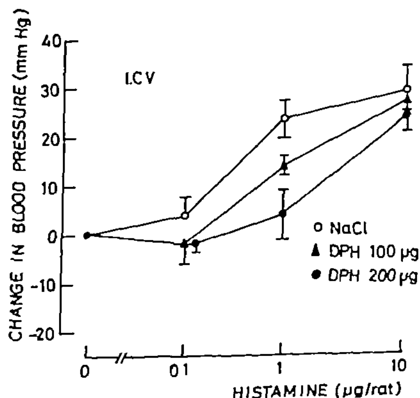


Fig 1 Effect of intracerebroventricular administration f histamine on blood pressure in urethane-anaesthetised rats. Increasing doses of histamine were administered into the lateral cerebral ventricle at 30 -min intervals. The maximal rise in blood pressure after each dose was sed in the calculation of the results. Diphenhydramine hydrochloride 100 μg (▲) or 200 μg (●) intracerebroventricularly was given 30 min before the start of histamine administrations. Control rats (○) received saline instead of diphenhydramine The difference between the control and diphenhydramine (200 μg) groups was significant at the $p < 0.01$ level at the histamine dose of 1 μg. The number of rats was 7 in each group Vertical bars indicate m.

induced hypotension by the specific histamine H_2-receptor blocking drugs (6 9 10 12) suggest the presence of sympatho-inhibitory histamine H -receptors in the brain while the hypertensive effects of histamine and dimaprit do not support this view Since some α-adrenoceptor blocking drugs antagonise the hypotensive effect of clonidine (21) the ability of metiamide to block central sympatho-inhibitory α-adrenoceptors was studied by using α-methylnoradrenaline (α-MNA) an established agonist of central α-receptors (8 21) While α-adrenoceptor blocking drugs antagonise the central hypotensive effect of α-MNA (21) metiamide pretreatment (488 µg i.c.v.) clearly potentiated the α-MNA induced fall in blood pressure At the dose of 20 µg, α-MNA lowered the blood pressure on the average by 10 % in the control rats and by 30 % in the metiamide pretreated rats. The difference between the groups is significant at the $p < 0.01$ level At the α-MNA dose of 80 µg the fall in blood pressure was 15 % in the control rats and 40 % in the metiamide-pretreated rats ($p < 0.01$) Therefore it can be concluded that metiamide does not block the sympatho-inhibitory α-adrenoceptors in the brain. Moreover since metiamide pretreatment antagonises the hypotensive effect of clonidine but potentiates the hypotensive effect of α-MNA, it can hardly be maintained (21) that clonidine and α-MNA have the same mechanism of action in the central nervous system.

The fa lure of histamine to mimic the central hypotensive effect of clonidine suggests that metiamide and clonidine are able to affect i the brain some mechanism which is related to but not identical with histamine H_2-receptors. It has been shown that imidazole acetic acid which is a metabolite of histamine (20) and can also be formed via a transamination pathway from histidine (14 20) lowers the blood pressure in cats upon intracerebroventricular administration (19) In the urethane-anaesthetised rats imidazole acetic acid (30–390 µg i.c.) induced a dose-related fall in blood pressure. Metiamide (1 1 mg i.c.v.) significantly antagonised the hypotensive effect of imidazole acetic acid At the dose of 390 µg the fall in blood pressure was approximately 50 % in the control group and about 30 % in the metiamide group In this respect the central hypotensive effect of imidazole acetic acid mimics that of clonidine

It is premature to implicate a new class of cerebral receptors in the hypotensive effects of clonidine and imidazole acetic acid However the present results could be explained conviniently by imagining the existence of cerebral sympatho-inhibitory "imidazole receptors" An activation of these receptors would bring about a lowering of blood pressure. The hypertensive effect of metiamide could be explained by the blockade of tonically activated "imidazole receptors" The blockade of these receptors by metiamide might, in turn, imply that they are closely related to histamine H -receptors. According to the present hypothesis imidazole acetic acid would lower blood pressure by acting as a natural activator of the sympatho-inhibitory "imidazole receptors" The synthetic antihypertensive imidazoline compound clonidine would lso be able to activate these receptors.

The hypothesis of the role of histamine H and H_2-receptors as well as that of the "imidazole receptors" in the central control of blood pressure is summarized in Fig. 2 It should be emphasised that further studies are needed to elucidate the mechanisms by which imidazole acetic acid and clonidine lower the blood pressure and by which metiamide antagonises their effect. The concept presented here can only be used as a working hypothesis. I addition, since the histamine H_2-receptor agonist dimaprit appears to exert non-specific hypertensive effects, the cerebral H -receptors may in fact mediate hypotensive effects.

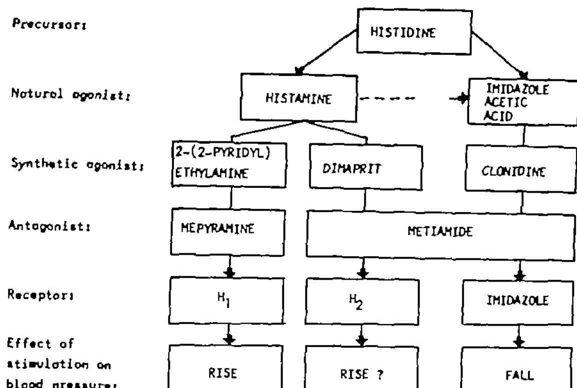


Fig. 2. Hypothesis of the role of histamine H_1 and H_2-receptors, and "imidazole receptors" in the central control of blood pressure. For further explanation, see the text.

ACKNOWLEDGEMENTS

This work was done under a contract with the Association of Finnish Life Insurance Companies It was also partly supported by a grant from the Paavo Nurmi Foundation *The skilful technical assistance of Mrs. Sirpa Rutanen Miss Tiina Heikkinen and Miss* Eila Pesonen is gratefully acknowledged We are much obliged to Mrs. Leena Pyykkö *and Mrs. Helena Saari for their efficient secretarial assistance*

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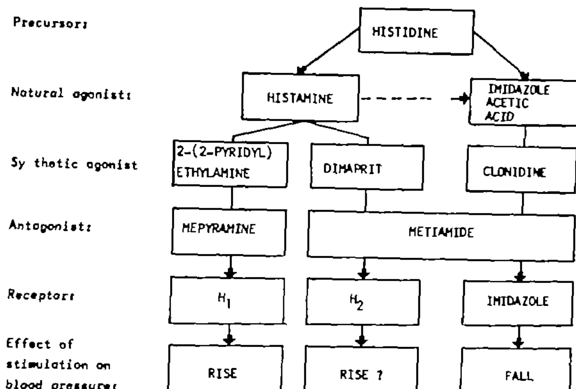


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MATERIAL AND METHODS

Fourt n patie ts (9 en nd wom) with es tial hyper tension to k part in the tudy Thei mean age w s 53 yea s (28 66 y ars) All p tients includ d were initially tre t d for t l t 5 w eks with diur tic agents only i e with out potassi suppl m nts Seven patients were tre ted with bendroflumethi zide 5 mg nc d ily 4 p tie ts with hydro chlor thiazide 50 mg once daily 2 patie ts with hlor- thalidone 50 mg once daily and 1 p ti t with mefru ide 50 mg o c daily

The p ti nts wer th gi n combi d therapy by adding aten lol 100 mg daily t th previ u diureti treatm nt f r n additi 1 5 week p ri d

M re e t f blood pr sure re don indi ectly u g s m ry sphyg m nomet (cuff rubb r bag 13 35 cm) Recumb t heart r te and blood pressu r r rded ft r mi tes f r st E t bl d press ure was recorded fter sta di g f r 2 m t s Di stolic bl od pre ur wa taken at th p int f d pp ar nc f the Kor tkoff so nd (ph se 5) El ctr lyt nd uri acid i erum and u ine we ea red on tw c ding days All m s rem nt were do n th h spit l b fo a d t the nd of the p riod of c mbin d th rapy

Stat st l n ly is as m d with Stud nt s t test for pai d d t

RESULTS

St ti ti ally significa t reductions of st nding nd recu bent

COMBINATION THERAPY WITH SALURETICS AND ATENOLOL IN ESSENTIAL HYPERTENSION.

Effects on blood pressure, electrolytes and uric acid.

Thorkell Gudbrandsson and Lennart Hansson

From the Department of Medicine Östra Hospital
University of Göteborg Göteborg Sweden

Saluretics and beta-adrenoceptor blocking agents constitute the most common types of antihypertensive therapy today As treatment of hypertension always is of a chronic nature side effects caused by treatment are of great importance The metabolic side effects seen during diuretic treatment namely hypokalemia and hyperuricemia are well known but their importance during chronic treatment is still a matter of some controversy (3 8)

Side effects during beta adrenoceptor blockade are to a great extent well known (5) Unwanted metabolic effects do occur but their clinical importance remains unclear However effects on electrolytes and uric acid have been considered unimportant (3) Recent investigations indicate that combined treatment with saluretics and a beta-adrenoceptor blocking agent may be of interest in this respect (6 7)

The purpose of the present investigation which is an open pilot study was to study effects on electrolytes and uric acid during combined treatment with saluretics and the beta-1-selective adrenoceptor blocker atenolol

MATERIAL AND METHODS

Fourt n pati nts (9 en and 5 women) with essential hyper t nsion t k part in the study Th ir me n ag was 53 years (28 66 years) All patient included were initi lly treated for at l ast 5 weeks with diuretic agents nly i e with o t p t ssium upplements Seven p tie ts er tr ated with be drofl m thi zid 5 mg o ce daily 4 patient with hydr chlor thiazid 50 mg onc d ily 2 patients with chlor th lid 50 mg once daily and 1 pati t with mefruside 50 mg ce d ily

Th pati ts re then gi ombin d th r py by dding t olol 100 mg d ily to th previous diuretic tr atment for an dditional 5 week p i d

M as rements of blood pr ure r done i directly sing mercu y sphyg m o eter (uff r bber b g 13 x 35 cm) Re bent h rt te and blood p ssur wer rec rded fter 5 minut s of st E t bl d pr sure was recorded fter t ding for 2 min tes Di stolic blood pres ur was t k n t the p int f d pp r n of the Kor tkoff s nds (ph se 5) El tr lyt d uri a d in s rum nd urine er meas red n two cc di g d ys All me s rem nt w re d e th h pit l befo d t the end of th p ri d of c bin d th rapy

Statistical a alysi s m d with Student t-te t for paired dat

RESULTS

St tistic lly sig ific nt red ctions of standi g and ecumb nt

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this ffect h wever is not well studied and is ob iously q ite co ple It sh uld be noted that diuretic usually have q ite opposit ffects on th renin angiotensin system compared with beta adrenoceptor blockers In some patients this c uld b of great importanc e g patients with a poor response to diuretic treatment because of angiotensin II depending hypertension (2) Such p tients could be expected to respond favourably t combined treatm nt with luretics and beta adrenoc pt r blockers

The rel ti ely marked increa e of rum chlorid found in the pre t in estigation was unexpected a d is difficult to explain Th possible cli ic l importance of this change u certain s is the tend ncy t wards reduc d calcium excreti n in the urine

Wilc nd Mit hell ha e show that tenolol giv n as the ole ther py ca d ig ificant red ction of serum urate (7) On the other hand they obs rv d a marked incr se of r m r te fter c bined ther py with tenolol and bendro flum thi zid (7) With non elective bet adrenoceptor blocki g ag nts a cert in incr ent of seru ur te has been report d (4) al h n added to pre iou diuretic th r py (5) In the pre t tudy only mi r nd in ignificant incre s of r m ur te w s en d ring the combined tre t ent There fore it i p sible that ten l l differs from e g propr nolol in thi r pe t

I con l sio certain etabolic effect o rate and l tr lytes ha e b en d o str ted in the pres nt inv stig tion d ring co bin d ther py ith t n lol and diuretics The clinic l rele nce of th incr ase in e um potassium co ld be g red c d ri k f r cardiac arrhythmi s h r as th clinic l i porta ce of some of th oth r chang s remains to

blood pressure and heart rate were seen when atenolol was added to the initial saluretic regimen (Table I) As regards the biochemical parameters a small but statistically significant increase of serum potassium was obtained after the addition of atenolol Concomitantly with this urinary excretion of potassium tended to go down No changes of serum sodium occurred Serum chloride increased significantly whereas serum calcium was unchanged The reduction of calcium excretion in the urine was at the limit of statistical significance (p - 0 05) Serum urate tended to increase whereas urinary excretion of uric acid was unchanged (For full details see Table I)

Side effects were reported by 4 patients during combined treatment (fatigue 2 impotence 1 and vertigo 1) One patient developed temporary atrial fibrillation

DISCUSSION

It is well known that combined treatment with saluretics and beta-adrenoceptor blocking agents can normalize blood pressure in a great proportion of patients with hypertension Thus our finding of an additional antihypertensive effect when atenolol was added to the previous diuretic regimen was not unexpected

Atenolol has previously been shown to increase serum potassium (7) In the present study we have demonstrated this effect also during combined treatment with diuretics This effect is possibly due to the renin suppressive action which has been demonstrated for atenolol (1) The exact nature of

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Table I Effect on Blood Pressure (mm Hg) Heart Rate (beats/min) and Biochemical Variables (mean ± S E M)

		Saluretics	Saluretics + Atenolol	Difference	p <
Recumb Syst BP	(n 14)	169 ± 5 1	148 ± 5 2	-21 ± 4 8	0 001
Recumb Diast BP	(n 14)	100 ± 3 3	86 ± 2 3	-14 ± 3 3	0 001
Erect Syst BP	(n~14)	161 ± 5 5	135 ± 6 0	-26 ± 4 3	0 001
Erect Diast BP	(n_12)	102 ± 3 8	88 ± 3 2	-14 ± 3 4	0 002
Heart Rate	(n=14)	77 ± 4 1	63 ± 3 7	-14 ± 3 8	0 01
S-Potassium mmol/l	(n~12)	3 8 ± 0 09	3 9 ± 0 09	0 14 ± 0 06	0 05
S-Sodium mmol/l	(n 12)	139 ± 0 7	140 ± 0 7	1 0 ± 0 7	ns
S-Chloride mmol/l	(n 12)	98 ± 1 1	102 ± 1 5	4 ± 1 1	0 01
S-Calcium mmol/l	(n 12)	2 35 ± 0 03	2 33 ± 0 03	-0 02 ± 0 03	ns
S-Urate µmol/l	(n 12)	314 ± 21	335 ± 29	21 ± 18	ns
U-Potassium mmol/24h	(n 13)	76 ± 7	65 ± 6	-11 ± 9	ns
U-Calcium mmol/24h	(n 11)	5 0 ± 0 6	3 9 ± 0 4	-1 1 + 0 5	=0 05
U-Urate mmol/24h	(n~11)	3 1 ± 0 2	3 0 ± 0 3	-0 1 + 0 4	ns

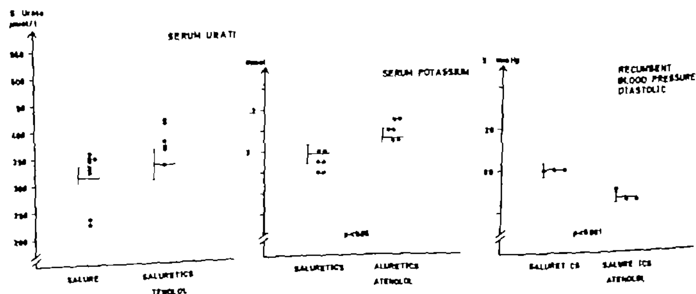


Figure 1

Some effects of combined therapy with saluretic nolol

artery using the Seldinger technique Continuous intra arterial measurement is then performed using a strain gauge transducer AE 840 (Aker Horten Norway) placed at the middel of the fore arm connected to an electro manometer (Simonsen & Weel Copen hagen, Denmark) Continuous flushing of the system with Hepari ne saline is performed using an Intraflow" unit (Anderson USA) The manometer is connected to a digital display unit from which systolic and diastolic BP can be read from pulse beat to pulse beat The manometer is further connected to a Memory Trendscope MTS 216 (Simonsen & Weel Copenhagen Denmark) where the intra arterial curve can be observed during the whole study The memo ryfunction of the oscilloscope has 120 points for systolic and 120 points for diastolic pressures The memory can be chosen to registrate blood pressure every 15 sec during ½ hous every 30 sec during 1 hour or every 120 sec during 4 hours In this stu dy mainly the two last registrations were used

Every hour or every third hour during the 24 hour registration the memory has to be emptied This is done very quickly (about 20 se conds) The recorded pressures are registrated on a writing unit (Mingograph Elema Siemens Sweden) When all 24 hours registra- tion has been performed the whole intra arterial curve can be con structed and average blood pressure for every hour can be calcu lated using optical intergration" From this curve mean daytime and mean nighttime BP (0 6 a m) can be calculated

Three to four times during the day repeated auscultatory and in tra arterial comparisons is performed in every subject using di rect registration of intra arterial BP and indirect measurements of right arm BP in order to establish the accuracy of auscultato ry BP in the single patient

The catheter is withdrawn on the morning at day 3 and meticulous compression of the puncture site is established in order to avoid any bleeding from the brachial artery The patient left the hospi- tal at day 3 for new repeated controlvisits at out patient clinic

RESULTS

The auscultatory BP decreased in nearly all subjects during hospi tal stay (Table I, Fig 1) The average decrease in systolic BP was 15 mm Hg and in diastolic BP 11 mm Hg In three of the subjects the decrease in diastolic BP was more than 20 mm Hg The average in tra arterial diastolic BP at daytime was in one of the borderline hypertensive subjects and 6 of the treated hypertensive subjects more than 20 mm Hg lower than diastolic BP at out patient clinic the mean difference of all subjects being 14 mm Hg for systolic BP and 18 mm Hg for diastolic BP The accuracy of auscultatory arm BP registration is given in Fig 1 (Third column for left) In the single patient the difference auscultatory intra arterial BP varied few mm Hg from time to time As a whole auscultatory systolic BP was 4 mm Hg lower than intra arterial systolic BP, while ausculta tory diastolic BP was 6 mm Hg higher In one of the 12 patients the re was a substantial difference in diastolic pressure of about 20 mm Hg In this patient BP at out patient clinic was in average 190/ 123 mm Hg auscultatory BP at hospital 179/104 mm Hg corresponding intra arterial BP 170/85 mm Hg, while mean daytime BP was about 180/90 mm Hg

With the present equipment it is possible to follow the intra arte

INTRA-ARTERIAL BLOOD PRESSURE MEASURED DURING 24-HOURS IN EVALUATION OF HYPERTENSIVE SUBJECTS

POUL EBBE NIELSEN & TAGE HILDEN
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DENMARK

Diagnosis of hypertension and the effect of antihypertensive treatment is based on measurements of auscultatory arm blood pressure (BP) during repeated visits to out-patient clinic i e repeated casual blood pressures In these indirect measurements two main problems are included 1 discrepancy between auscultatory BP and intra-arterial BP 2 discrepancy between casual BP measured at out-patient clinic and mean BP of the unobserved patient during daily life activities
When several studies has been published concerning the accuracy of auscultatory BP tested against intra-arterial measurements (conf 4) only few investigations have delt with the fundamental problem of casual BP tested against daily life BP in hypertensive subjects Using semiautomathical equipment for repeated indirect measurements of arm BP Irwing & al (1) as well as Sokolow & al (6) demonstrated that casual BP tended to be much higher than the mean BP measured repeatedly during daytime while Lund-Johansen (3) demonstrated good agreement between casual BP and mean daytime BP Using continuously intra-arterial registration of BP during daily life activities Littler & al (2) demonstrated in few patients with hypertension WHO-group I that casual BP was significantly higher than mean daytime BP while good agreement was found in a group of treated hypertensive subjects
In our study we have compared casual BP to intra-arterial BP measured during 24-hours on hospital in a group of borderline hypertensive subjects as well as a group of badly controlled hypertensive patients Furthermore we performed in each subject repeated comparisons between auscultatory and intra-arterial blood pressures

MATERIAL AND METHOD

The patients studied were (Table I) 1 Four untreated borderline hypertensive males aged 25 to 51 years with diastolic BP (Phase V) at out-patient clinic between 95 and 108 mm Hg 2 Twelve treated hypertensive subjects with essential hypertension (8 males 4 females) aged 42 to 68 years with DBP ≥ 105 mm Hg during repeated measurements at out-patient clinic The antihypertensive therapy was different from patient to patient but it was characteristic to all the patients in this group that the blood pressure was insufficiently controlled on antihypertensive therapy which often was given as combined therapy During the whole study the antihypertensive therapy was unchanged
All the subjects are followed at out patient clinic in several visits before and after the intra-arterial measurement in order to get a stable baseline for auscultatory BP Then the subjects are hospitalized for 3 days In the morning at day 2 the patient is placed comfortable in the bed and a 1 0 mm polyethylene catheter (Surgimed Ølstykke Denmark) is inserted in the left brachial

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DENMARK

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When several studies has been published concerning the accuracy of auscultatory BP tested against intra-arterial measurements (conf 4) only few investigations have delt with the fundamental problem of casual BP tested against daily life BP in hypertensive subjects Using semiautomathical equipment for repeated indirect measurements of arm BP Irwing & al (1) as well as Sokolow & al (6) demonstrated that casual BP tended to be much higher than the mean BP measured repeatedly during daytime while Lund-Johansen (3) demonstrated good agreement between casual BP and mean daytime BP Using continuously intra-arterial registration of BP during daily life activities Littler & al (2) demonstrated in few patients with hypertension WHO-group I that casual BP was significantly higher than mean daytime BP while good agreement was found in a group of treated hypertensive subjects

In our study we have compared casual BP to intra-arterial BP measured during 24-hours on hospital in a group of borderline hypertensive subjects as well as a group of badly controlled hypertensive patients Furthermore we performed in each subject repeated comparisons between auscultatory and intra-arterial blood pressures

MATERIAL AND METHOD

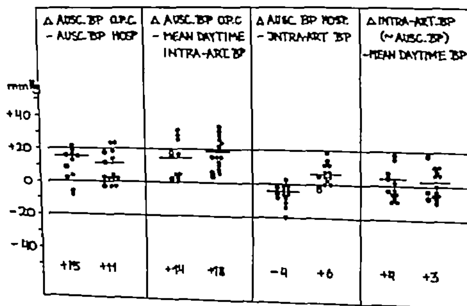
The patients studied were (Table I) 1 Four untreated borderline hypertensive males aged 25 to 51 years with diastolic BP (Phase V) at out-patient clinic between 95 and 108 mm Hg 2 Twelve treated hypertensive subjects with essential hypertension (8 males 4 females) aged 42 to 68 years with DBP ≥ 105 mm Hg during repeated measurements at out-patient clinic The antihypertensive therapy was different from patient to patient but it was characteristic to all the patients in this group that the blood pressure was insufficiently controlled on antihypertensive therapy which often was given as combined therapy During the whole study the antihypertensive therapy was unchanged

All the subjects are followed at out-patient clinic in several visits before and after the intra-arterial measurement in order to get a stable baseline for auscultatory BP Then the subjects are hospitalized for 3 days In the morning at day 2 the patient is placed comfortable in the bed and a 1 0 mm polyethylene catheter (Surgimed Ølstykke Denmark) is inserted in the left brachial

TABLE I
Blood Pressure (mm Hg) measured by Auscultation at Out Patient Clinic (O P C) compared to Intra arterial Blood Pressure measured during 24 hours at Hospital

	An BP t O P C b f e and fter Admittanc to Ho pital		BP at Hospital			
			Au BP compared t I tra t BP		I tra rt BP	
	B f e	After	Ausc BP	I tra rt BP	Average BP at daytime	Av rag BP t night
Bord rline mean	159/99	152/98	146/91	153/89	145/85	119/73
Hype tensiv rang n 4	152/95 170/108	135/92 165/106	128/85 168/97	136/83 169/98	138/80 150/90	110/65 130/80
T eated Hypertensive						(n 7)
DBP > 10% mmHg m an	192/118	180/111	179/108	184/102	183/99	163/92
12 rang	170/105 230/135	160/95 223/137	132/78 217/132	145/81 226/128	140/70 220/122	130/80 215/110

FIG 1
Individual difference of systolic and diastolic blood pressure (left respectively right columns) recorded in 4 borderline hypertensive subjects (open circles) and 12 treated hypertensive subjects Further information see the text O P C = out patient clinic



rial BP during unobserved as well as observed state ex when nurses or doctors are comming into the room in order to measure the auscultatory BP
In the main group of investigated subjects there was almost no difference between intra-arterial BP when the patients was observed compared to unobserved condition (Fig 1 right column) However in two of the patients it was evident that the simple procedure of auscultatory measurement was sufficient to give a rise in intra-arterial BP (Fig 1)
In a 51-year old man with borderline hypertension auscultatory BP at out-patient clinic was in average 170/95 mm Hg auscultatory BP at hospital 168/97 mm Hg corresponding intra-arterial BP 169/98 mm Hg while mean daytime BP was 145/80 mm Hg The other patient was a 52-year old female auscultatory BP at out-patient clinic 230/135 mm Hg at hospital 217/121 mm Hg corresponding intra arterial BP 218/114 mm Hg while mean daytime BP was about 190/100 mm Hg BP during night was in the borderline hypertensive in average 119/73 mm Hg - in several hours during sleep even much lower Among treated hypertensive subjects a decrease was also found (Table I) but only among the patients where sleep was observed

DISCUSSION

In this study we have compared measurements at out-patient clinic to measurements during hospitalization with all subjects in supine position during the 24 hours It might there fore be argued that our measurements are not comparable to earlier investigations where the patients are tested during daily life activities This might explain our big difference between BP at out-patient clinic and mean daytime intra-arterial BP We have mainly used the present measurements to test the single patient on two points a accuracy of auscultatory BP against intra-arterial BP b BP during unobserved conditions compared to observed conditions If no substantial difference is found in the single patient we feel it is justified to increase the antihypertensive therapy in order to get the casual BP sufficiently controlled Contrary if big differences exists these differences should be taken into account when therapy is discussed As mentioned we demonstrated in one subject a big inaccuracy of auscultatory BP compared to intra-arterial BP ad in two subjects a big difference between intra-arterial BP during unobserved and observed condition No severe complications to the intra-arterial procedure were observed We have tried to correlate our findings to hypertensive organ damages but in this small group of subjects we were unable to find any correlation to organ damages
At last a citation from G Pickering (5)
"What we can say then is that the arterial pressure as measured in the clinic is a useful measurement so long as the doctor does not depend too slavishly upon it or give it greater significance in assessing the patients condition than it deserves

ACKNOWLEDGEMENT

The study was supported by grants from Carlsberg Mindelegat and Det Lægevidenskabelige Fond for Stor-København Grønland og Færøerne

RENIN ANGIOTENSIN SYSTEM AND SYMPATHETIC NERVE ACTIVITY IN MILD ESSENTIAL HYPERTENSION. THE FUNCTIONAL SIGNIFICANCE OF ANGIOTENSIN II IN UNTREATED AND THIAZIDE TREATED HYPERTENSIVE PATIENTS.

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INTRODUCTION

Measurement of plasma renin a tivity on blo d ample from patient with essential hypertension and normot nsive ontrols have led to cla sificati n of pati nts with e sential hypertension int renin- ubgroup (1 2) This approach has not settled the role of angi t nsin II in the maintenan f hypertension By means of pe ific competitive inhibitor of angiot nsin II e g saralasin it i now po ible to asses the participation of angiotensin II in hypert nsi n in a more direct way

The rol of the sympath tic nervous system has al o been a subj t f ntinuing debate Whereas ome inve tigators hav found in reas d plasma at cholamine onc ntrati n in ntial hypert nsi n thi ha been refuted by thers (4)

Th aim of the present tudy ha be n to inve tigate by means of arala in the fun tional signifi an e of the renin-angi tensin sy t m (RAS) in the maintenance f high blood pre sure in a homogenou group f patient with mild e sential hypert nsion and measure plasma n radrenaline c ncentrati n in the ame group of pati nt

PATIENTS AND METHODS

25 pati nt (7 F 18 M) with e ntial hyperten ion (WHO I) identifi d during a survey of a population born in 1936 were inve tigat d Non f the pati nt had ever recieved antihypertensiv treatment 25 f rty-y ar old normot nsive individuals (1 F 15 M) le ted from the ame populati n rved a a c ntrol group Plasma renin onc ntration (PRC) plasma angiot nsin II n ntration (PA II) plasma aldo t rone conc ntration (PAC) and plasma n radrenaline con ntration were measured in the odium replet tat supine at rest and after intravenous admini tration of furo emide with sub quent qui t ambulation Plasma volume (PV) and exchange bl odium (Na_E) were also determined in the odium repl t state

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6 Sokolow, M & al Circulation 1966 34 279-297

Treatment with hydro hlorothia ide rev aled that the group of hypert naive could be divided into 11 thiazide-re ponders and 10 thiazide-nonresponders with a fall in diastolic blood pre ure f 10 mm Hg or more during treatment as the criterion In the group f respond re y tolic blood pre sure changed from 151 mm Hg (131-184) to 134 (120-145) and diastoli blood pressure d creased from 106 (98-113) to 92 (84-98) while in th 10 non-respond rs syst lic and diastolic bl od pre sure was 147 mm Hg (131-184) and 103 mm Hg (95-111) re pe tively before treatment only changing insignificantly on thiazide

During treatment PV d creased ignificantly 3-4% on average th decrea being imilar in thiazid -resp nd rs and n nre pon-der Na_E did n t hange ignificantly Although th natriureti eff ct is of importanc for the antihyperten ive action of thiazi-d thi could n t explain th antihypertensive response sin c hange in PV and Na_E were imilar in thiazide-responders and n nre ponder

The d terming fa tor for the quantitative bl od pre sure response to thiaz detreatment proved to be th re ponsivens of the renin-angiot nain sy t m Thi on lu ion i upported by the much high r PRC and PA II valu s in thiazide n nre ponders a om-pared to thiazide-re ponders During treatment PRC was 96 mIU/l (71 262) in the group of nonresponder and 49 mIU/l (35-142) in re pond r ($p < 0\ 02$) Similarly PA II was 37 pmol/l (23-61) and 26 pmol/l (14-41) ($p <\ 05$) PAC did n t differ in the two groups Th importan e f the RAS merge even more c nvincing from th out ome of th aralasin infusions in th thiazide-treat d pati nt howing that all thiazide-nonre ponders xhibit d a l ar-cut de rease in MAP while only 4 out of 11 thia ide-re ponders howed a borderline decreas There wa a lo invers rrelation betwe n change in MAP during aralasin infu ion and pre infu i n l vel f PA II ($r = -0\ 70$ $p < 0\ \ 1$) the fall in MAP being more pronounced when pre-infu ion PA II wa high Furthermore whereas supine re ting PRC and PA II value bef re treatment did not differ in th two group of pati nt pre treatment furo emide- timulated PRC and PA II were higher in th group of thia ide-nonresponders a ompared t thiazide-re ponders PRC being 84 mIU/l (42-162) and 41 mIU/l (14-106) in nonre ponders and re pond rs respectively ($p < 0\ 05$) Similarly PA II wa 37 pmol/l (12 72) and 14 pmol/l (6-32) ($p < 0\ \ 5$) PAC did not diff r in the two group f patient

(o 54 - 5 4 nmol/kg/min) was carried out in supine position in the sodium replete state Blood pressure (arteriosonde 1217) was recorded at 2 min intervals during a 3o min control period during 35 min of saralasin infusion and during 3o min after cessation of infusion

21 patients were treated with hydrochlorothiazide mean dose 75 mg/day for 3 months and the examinations were repeated Figures are presented as median values with range in brackets

RESULTS AND DISCUSSION

In the group of hypertensive patients PRC PA II and PAC supine at rest did not differ from reference values in the 4o year old normotensive subjects Values after acute stimulation were also nearly identical Thus within this frame of reference a clear-cut division of the present homogenous group of patients with mild essential hypertension into renin subgroups did not emerge In accordance with the proposal that low renin hypertension reflects a stage in the development of essential hypertension and not a distinct entity (3) a classification into renin- or angiotensin-subgroups may well tend to disappear when age duration and severity of hypertension are identical

Normal values of PRC and PA II per se do not exclude the implication of RAS in the maintenance of hypertension However in the untreated sodium replete state angiotensin II blockade by means of saralasin only caused a significant decrease in mean arterial pressure (MAP) in two out of twenty-five patients and in the group as a whole MAP actually increased from 1o8 mm Hg to 111 mm Hg ($p < o\ o5$) Similarly an agonistic effect of saralasin on adrenal receptors was discovered as PAC increased by 12o% across saralasin infusion ($p < o\ o1$) Apparently in mild essential hypertension angiotensin II has no decisive role in the maintenance of high blood pressure

Based upon a positive correlation between age and plasma catecholamine concentration some investigators have claimed that elevated plasma catecholamine levels in patients with essential hypertension could be explained by age differences between the hypertensive patients and the normotensive controls (4) However this point

Treatm nt with hydrochlorothiazid revealed that the group of hypert nsive could be divided int 11 thia ide-re ponders and 1 thiazide nonre pond rs with a fall in dia tolic bl od pre sure of 1 mm Hg or more during treatment as the criteri n. In the group of responder sy tolic blood pre sure changed from 151 mm Hg (131-184) t 134 (12o-145) and dia tolic blood pre ure d crea ed from 1o6 (98-113) to 92 (84 98) while in the 1o non-re pond rs sy t lic and dia tolic blood pre ure was 147 mm Hg (131-184) and 1o3 mm Hg (95-111) re pectively before treatment only changing insignificantly on thiazide

During treatment PV d creas d ignifi antly 3-4% on average the d creas being imilar in thiazide-re pond rs and n nre pon-d r Na_E did n t change ignifi antly Alth ugh th natriuretic eff t i f importance f r the antihypertensive action of thia i-d s thi could n t explain the antihypert nsive response sin hange in PV and Na_E were imilar in thiazid -re pond rs and nonre pond rs

The d t rming fa t r f r the quantitative bl od pre sure response to thiazid treatment proved to be the re ponsivenes of the renin-angiot nsin sy tem Thi con lusion i support d by the much higher PRC and PA II valu in thiazid n nre ponders as com-pared t thiazide-re pond rs During treatment PRC was 96 mIU/1 (71 262) in the group of nonresponders and 49 mIU/1 (35-142) in re pond rs (p < o2) Similarly PA II wa 37 pmol/1 (23-61) and 26 pm 1/1 (14-41) (p < o o5) PAC did not differ in th two groups The importan e of the RAS emerge even more c nvin ing from the outcome of the aralasin infusions in the thiazide-treated pati nt howing that all thiazide nonresponders xhibited a lear cut de reas in MAP while only 4 out of 11 thiazid re pond rs howed a borderline decrea Th re wa a l se inver rrelation betw n change in MAP during arala in infu ion and pre-infu ion l vel of PA II (r = -o 7o p < o oo1) the fall in MAP being more pronoun d wh n pre-infusi n PA II was high Furthermore whereas supine re ting PRC and PA II values bef re treatment did n t differ in the two group of pati nt pre treatment furo emid - timulated PRC and PA II were higher in the group f thi ide nonre pond r a compared to thiazide-re pond rs PRC being 84 mIU/1 (42-162) and 41 mIU/1 (14-1o6) in nonre ponders and re ponders re pe tively (p < o o5) Similarly PA II wa 37 pmol/1 (12 72) and 14 pmol/1 (6-32) p < 5 PAC did n t differ in the two groups of pati nts

Although the patients could not be classified into low-normal-high renin subgroups, it is pertinent that they showed hypo-normo- and hyperresponsiveness of the renin-angiotensin system Thus acutely stimulated PRC and PA II could to some extent predict the subsequent response to chronic thiazide treatment Several counter-regulatory mechanisms might be operative during thiazide treatment, e g the sympathetic nervous system During treatment plasma noradrenaline concentration increased slightly to a similar degree in both "thiazide-nonresponders and thiazide responders" Consequently differences in sympathetic nerve activity, as defined from measurements of plasma noradrenaline concentration did not explain differences in the blood pressure response to thiazide treatment

CONCLUSION:

In mild untreated essential hypertension angiotensin II has no decisive role in the maintenance of high blood pressure The functional significance of RAS emerges after thiazide treatment Thiazide-induced stimulation of RAS counterbalances the hypotensive effect of thiazide in some 40% of the treated patients Thus the responsiveness of RAS determined the quantitative blood pressure response to treatment Pre-treatment furosemide-stimulated PRC and PA II to some extent predicted the subsequent response to thiazide treatment

ACKNOWLEDGMENT

We would like to thank Dr Michael C L Cox Eaton Laboratories Norwich New York for generous supplies of saralasin

TABLE 1 Plasma renin concentrati n (PRC) angiotensin II onc ntration (PA II) aldo terone conc ntration (PAC) and n radrenaline con entration (PNC) at re t supine and aft r furo emide + ambulation (Median value and range in bracket)

		Es ential hypertensi n n = 25		Normotensive controls n = 25
PRC(mIU/1)	Rest Supine	29(11-67)	n s	31(11-49)
	Furo +Amb	57(14-162)	n s	78(17-225)
PAII(pm 1/1)	Re t Supine	8(4-22)	n	10(4-20)
	Furo +Amb	26(6-72)	p<o o5	35(12-91)
PAC(pmol/1)	Rest Supine	195(56-417)	n	167(111-361)
	Furo +Amb	556(56-1446)	n.s	667(222-2029)
PNC(nmol/1)	R st Supine	1 27(o 51-2 o4)	n s	1 21(64-2 29)
	Furo +Amb	2 36(o 96-3 50)	n.s	2 36(1 46-4 01)

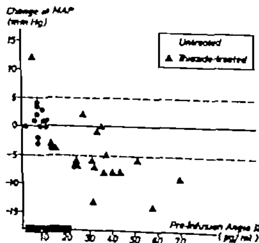


Fig. 1
Change in MAP on aralasin infusion in relation t pre-infusion pl sma angi t nsin II con ntration (pg/ml∼ pmol/1) in patient with e sential hypert nsi n

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EFFECT OF SODIUM LOADING ON THE RENIN ALDOSTERONE SYSTEM IN ESSENTIAL HYPERTENSION

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I troduction

In essential hypertension a sodium load is excreted more abruptly than in normotensive subjects Some studies have shown an abnormal sustained aldo terone secretion during salt loading in es ontial hypertension The purpose of the present investigation has been to study the relationship between the renin-aldosterone system and the urinary sodium excretion during sodium loading in young patients with mild essential hypertension and normotensive control subjects

Material and methods

Fifteen patients 11 male and four female mean age 28 years (range 21-36) with mild es ential hypertension (mean blood pressure=121^{+}3 (1SEM)mm Hg) were studied All drugs were discontinued for at least 6 weeks before the studies were performed Ten healthy normotensive control ubjects five male and five female mean ge 29 years (range 22 44) (mean blood pressure=92$\pm$2(1SEM)mm Hg) we e studied

Blood samples for determination of plasma renin concentration (PRC) and plasma aldo terone concentration (PAC) were drawn in the morning after the end of a 40 min control period and after the intrav nous infusion of 500 ml of sodium chloride solution (50 g/l) giv n over 40 min Urine was collected for the determination of sodium in the control period and the infusion period

PRC was determined by the method described by Giese et al (1) and PAC by Nielsen s method (3) Blood pressure was measured by

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EFFECT OF SODIUM LOADING ON [illegible]

ESSENTIAL HYPERTENSION

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Introduction

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sphygmomanometer technique Non-parametric tests were used for the statistical analysis

Results

Changes in PRC and PAC during sodium loading are shown in fig 1

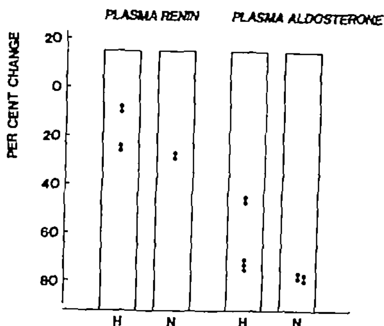


Fig 1 Changes in PRC and PAC during sodium loading in patients with essential hypertension (H) and normotensive control subjects (N)

In the hypertensive group the mean PRC fell significantly from 43 uGU/ml to 29 uGU/ml ($p < 0\ 01$) and the mean PAC from 16 5 ng/100 ml to 5 7 ng/100 ml ($p < 0\ 01$) during sodium loading In the normotensive group the mean PRC fell from 34 uGU/ml to 24 uGU/ml ($p < 0\ 01$) and the mean PAC from 13 8 ng/100 ml to 5 8 ng/100 ml ($p < 0\ 01$) The fall in PRC and PAC in the hypertensive group did not differ significantly from the fall in the normotensive group

The percentuel increase in mean blood pressure was the same in the hypertensive (5%) and the normotensive group (4%)

The increase in urinary sodium excretion in the hypertensive croup (9 75 mmol/40 min) was significantly higher ($p < 0\ 05$) during saline infusion than in the normotensive group (5 12 mmol/40 min)

PRC and PAC were significantly correlated in both the hypertensive (rho=0 72 $p < 0\ 01$) and the normotensive group (rho=0 80 $p < 0\ 01$) before but not after sodium loading

The rise in urinary sodium excretion during sodium loading in the hypertensive patients was significantly correlated with the suppression of PAC (rho=-0 59 $p < 0\ 05$) but not with the fall in PRC Changes in urinary sodium excretion in the normotensive subjects were not correlated with changes in PAC or PRC

Di cussion and conclusion

The results indicate that the suppressibility of the renin-aldosterone system by hyperosmotic saline is normal in young patients with mild es ential hypertension The disagreement with other studies which showed an abnormal aldosterone secretion pattern during sodium loading could be attributed to differences in the amount of sodium given the manner and duration of loading and to the fact that many patients studied previously were older and suffered from more pronounced hypertensive vascular disease (2) The rose in urinary sodium excretion with decreasing PAC suggests that PAC might be a regulatory factor in exaggerated natriuresis in young patients with mild essential hypertension

R ferences

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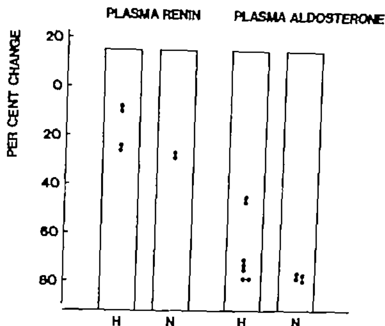


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The results indicate that the suppressibility of the renin-aldosterone system by hyperosmotic saline is normal in young patients with mild essential hypertension The disagreement with other studies which showed an abnormal aldosterone secretion pattern during sodium loading could be attributed to differences in the amount of sodium given the manner and duration of loading and to the fact that many patients studied previously were older and suffered from more pronounced hypertensive vascular disease (2) The rose in urinary sodium excretion with decreasing PAC suggests that PAC might be a regulatory factor in exaggerated natriuresis in young patients with mild essential hypertension

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AFFERENT ARTERIOLAR DIAMETER IN DOCA-HYPERTENSIVE AND POST-DOCA HYPERTENSIVE RATS ESTIMATED BY MEANS OF MICROSPHERES

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The main intent of this study was to estimate afferent arteriolar diameters (d_{AA}) i 4 different groups of male albino Wistar rats: normal controls heminephrectomized controls DOCA NaCl hypertensive rats and post-DOCA hypertensive rats

MATERIAL AND METHODS

The animals were fed on standard pellets The hypertension was induced by the subcutaneous implantation of 75 mg desoxycorticosteronacetat (DOCA) and substituting drinking water with 1% of NaCl in water These animals were studied 53 - 211 (mean 111) days after the implantation Heminephrectomia and DOCA-implantation were done in ether narcosis In the post-DOCA group the DOCA-pellet was removed 119 days after implantation and in the following 16 days until the microspheres were injected the 1% of NaCl was substituted with ordinary tap water The systolic blood pressure was measured with regular intervals by means of a tail cuff The DOCA-hypertension started to develop in about 20 days with a slow further increase in the blood pressure until a stable niveau was reached about 50 - 60 days after implantation of the DOCA-pellet

A specially designed microsphere diameter distribution was obtained after repeated edimentation in water of two stock solutions with nominal diameters 15 ± 5 and 25 ± 5 μm A small sample of ^{141}Ce-labelled 15 μm microspheres was added The diameters ranged from 10 to 35 μm in the final solution Prior to injection the suspension was vigourously shaken and ultrasound was used to break aggregates between the microspheres

Th animals were anaesthetized with an intraperitoneal injection of Nembutal Natrium® (50 mg/kg) and the trachea was cannulated Systemic arterial blood pressure was measured via a PE-50 catheter introduced through the left common carotid artery and advanced to the aortic arch This catheter which had its distal end sealed off and was supplied with circumferential sideholes was also used for the injection of the microspheres (injection time 10 - 15 s) Renal blood flow (RBF) was measured by the reference sample technique

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The heminephrectomized animals had a lower body weight and a significantly higher kidney weight ($P < 0.001$) than the normal controls but blood pressure RBF and $d_{AA\ dist}$ were not significantly different The systolic blood pressures (SAP) in DOCA-NaCl hypertension and in post DOCA hypertension were not significantly different during the experiment but a significant increase had taken place when comparing with the normal and hemineprectomized controls ($P < 0.005$) The renal blood flows were not significantly different for any of the four groups

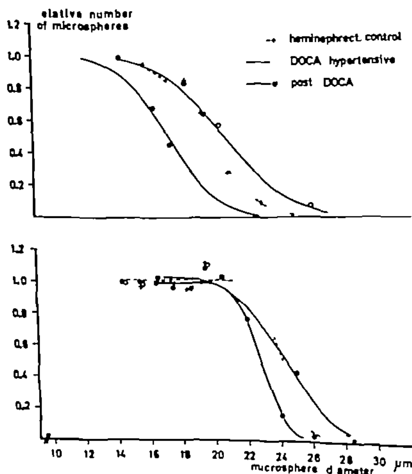


Figure 1 Relative entrance of microspheres into glomeruli (upper panel) and into afferent arterioles (lower panel) as a function of microsphere diameter The curves for the normal control (not shown here) were lying close to those of the heminephrectomized control

A reference blood flow of 10 μl/s was withdrawn for about 45 s through a PE-10 catheter placed in one femoral artery The systemic circulation was abruptly stopped by the intravenous injection of concentrated KCl at about 70 - 90 s after the microsphere injection was started The kidneys were removed weighed put in 4% formaline in phosphate buffer and the radioactivity was counted in a well counter Tissue sections of 30 μm thickness were stained with hematoxylin-eosin and mounted for microscopical examination The maximal visible diameter of the microspheres as well as their anatomical positions (glomerular in afferent arterioles in interlobular arteries) were recorded The relative number of microspheres entering the afferent arterioles and the relative number of microspheres passing from afferent arterioles into the glomeruli were calculated as a function of microsphere diameter (Figure 1) These curves were calculated uncorrected and when correcting for section thickness (1) The mean values and the standard deviations in the diameter distributions of the proximal and the distal part of the afferent arterioles were then estimated by means of nonlinear regression analysis of these microsphere entrance curves (2) In addition the flow conductance ratio (FCR) relative to the normal controls was calculated

RESULTS AND DISCUSSION

Table 1 Experimental data Values denoted by an † are corrected for section thickness (mean ± SEM)

	Normal controls	Heminephrect controls	DOCA-NaCl hypertensive	post-DOCA hypertensive
No of rats	4 (8 kidneys)	5	6	5
Body wt (g)	317 ± 11	253 ± 19	308 ± 19	322 ± 17
Kidney wt (g)	98 ± 03	1 43 ± 06	2 39 ± 19	2 05 ± 12
SAP (mmHg)	154 ± 4	156 ± 9	219 ± 10	210 ± 11
RBF (ml/min/g)	2 73 ± 23	3 27 ± 69	2 90 ± 53	2 94 ± 47
d_{AA} dist (μm)	19 3 - 19 2†	19 8 - 20 3†	17 0 - 17 4†	20 5 - 20 8†
	1 00	1 05 - 1 16†	61 - 65†	1 28 - 1 36†

The heminephrectomized animals had a lower body weight and a significantly higher kidney weight (P< 0 001) than the normal controls but blood pressure RBF and $d_{AA\ dist}$ were not significantly different The systolic blood pressures (SAP) in DOCA NaCl hypertension and in post-DOCA hypertension were not significantly different during the experiment but a significant increase had taken place when comparing with the normal and heminephrectomized controls (P< 0 005) The renal blood flows were not significantly different for any of the four groups

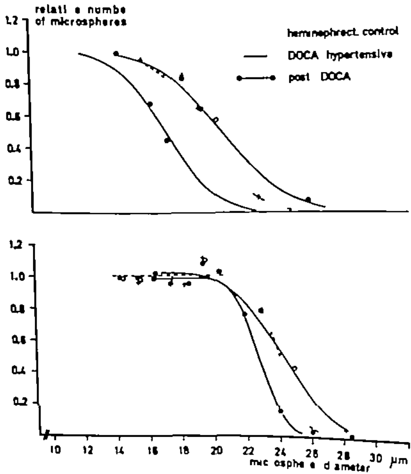


Figure 1 Relative entrance of microspheres into glomeruli (upper panel) and into afferent arterioles (lower panel) as a function of microsphere diameter The curve for the normal control (not shown here) were lying close to those of the heminephrectomized control Correction for section thickness (30 µm) has been made

The most prominent changes were a significantly smaller $d_{AA\ dist}$ in DOCA-NaCl hypertension than in the normal and heminephrectomized controls ($P < 0\ 001$) and a significantlv larger $d_{AA\ dist}$ in post-DOCA hypertension than in DOCA-NaCl hypertension The parameter $d_{AA\ dist}$ in post-DOCA hypertension was even signficantly larger than for the normal and heminephrectomized controls ($P < 0\ 05$)

Combining this with the flow and pressure data in Table I one may conclude that in DOCA-NaCl hypertension the afferent arteriole and especially its distal part is constringed to increase preglomerular resistance and maintain a reasonable glomerular perfusion pressure In the post-DOCA hypertension one may suggest that the interlobular artery is constringed since we found the afferent arteriole dilated which may be a secondary autoregulatory response Our findings thus give support to the hvpothesis that hypertension induced changes in the interlobular artery reduce the afferent arteriolar perfusion pressure and provoke an autoregulatory dilation of the afferent arteriole The hypertension is then transformed from a normal renin to a high renin hvpertension

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SODIUM BALANCE AND STRUCTURAL VASCULAR CHANGES IN THE KIDNEY DURING DEVELOPMENT OF HYPERTENSION IN SPONTANEOUSLY HYPERTENSIVE RATS

By

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INTRODUCTION

The mecha isms leadi g to p imary hypert nsio i ma and in genetically hypertensive rats e still poorly understood The spontaneously hyperte ive rats (SHR) display igns of increa ed sympathetic acti ity (10) while plasma volume i normal or lightly lowe ed (11) I the Mil hypo tensive trai of ats (MHS) the pre sure i e is howeve ssoci ted with sodium ret ntion nd pl sma olume increase (2) I addition tudi In SHR have demonstrated adaptive increases i wall/lume rati of the p eglomerul sistance vessels leading to increased en l a cula resi tance i the stablished pha of hype tension (8) I senti l hypert sion i ma there idence of reduced ability to excrete salt nd wate as well a of a incr ased enal vasc l si t nce with increasing seve ity of hype tension (1) Thus both i ma nd rats the p og es ion of hypertension i accompa i d by a inability to handl sodium as well as g adual incre se i renal vascula resist nce The pre t tudy was therefore und rtaken to investigat if th prog e ively developing st uctu al vas l changes withi th kidney co t ibut to the impai ed renal handli g of sodium or if these two f ctors t i dependently f each othe

MATERIAL AND METHODS

Expe iment were pe formed on 7 nd 16 weeks old spontaneously hyp rt sive rat (SHR) (10) nd matched normotensive control Wista ts (NCR) Wi ta Koyt ts (WKR) aged 16 weeks were lso used as cont l Each g oup consisted of 10 t At 7 weeks of age SHR had 10 % highe blood press re than NCR Thi difference i creased t ound 25 % at 16 week of ge Th a imals sed in balance studies were placed in indi idual metabolic cages Aft t days of adaptation the balance studies were performed du i g nothe ten day pe iod during

The most prominent changes were a significantly smaller $d_{AA\ dist}$ in DOCA-NaCl hypertension than in the normal and heminephrectomized controls ($P < 0\ 001$) and a significantlv larger $d_{AA\ dist}$ in post-DOCA hypertension than in DOCA-NaCl hypertension The parameter $d_{AA\ dist}$ in post-DOCA hypertension was even signficantly larger than for the normal and heminephrectomized controls ($P < 0\ 05$)

Combining this with the flow and pressure data in Table 1 one may conclude that in DOCA-NaCl hypertension the afferent arteriole and especially its distal part is constringed to increase preglomerular resistance and maintain a reasonable glomerular perfusion pressure In the post-DOCA hypertension one may suggest that the interlobular artery is constringed since we found the afferent arteriole dilated which may be a secondary autoregulatory response Our findings thus give support to the hvpothesis that hypertension induced changes in the interlobular artery reduce the afferent arteriolar perfusion pressure and provoke an auto-regulatory dilation of the afferent arteriole The hypertension is then transformed from a normal renin to a high renin hypertension

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SHR aged 16 weeks showed an increased sodium retentio only when calculated per g am body weight

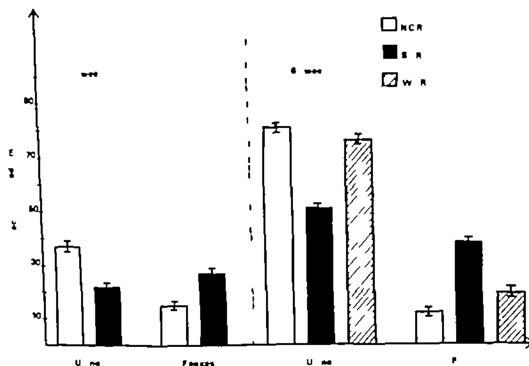


Fig 1 F actional exc tion of odium by the kidneys nd the g st i t stinal t t

U inary ldost rone once t ation was ot sig ifica tly different betwoe SHR and NCR t 7 week of ge b t at 16 weeks it was igni fi tly incre sed i SHR (NCR 4 5 ± 0 1 umol/day SHR 9 1 + 1 5 umol/day p < 0 05) PRA was ignificantly lowe i SHR aged 16 weeks the i NCR (NCR 4 5 0 5 ng/ml/h SHR 1 9 0 3 ng/ml/h p < 0 05) No st ti tical analyse were pe formed t 7 week of ge due to low umbe of observations (5) but the fig re for PRA was lowe fo SHR ve t thi age No significa t diff rences i nor drenaline excretion were found betwee SHR and NCR t any age

The hemodynami tities of tructural asc l changes incre sed re istance t ma imal dil t tion a increas d steepnes of the resis tance curve and an i a d ma imal pres or response b came more

sodium excretion were measured In addition urinary aldosterone and noradrenaline were determined Body weight was measured every third day After the balance period the arterial blood pressure was measured in the awake animals via a canula inserted into the tail artery during brief ether anaesthesia The rats were than decapitated during a brief ether anaesthesia and blood samples for plasma renin activity (PRA) were collected from the carotid artery Urinary aldosterone was measured with a radioimmunoassay kit from NEN and urinary noradrenaline was analysed with a modified method according to von Euler and Floding (4) PRA was analysed using a radioimmunoassay for angiotensin I (7)

In separate groups of agematched SHR and NCR the isolated renal vascular beds were pairwise perfused with an artificial plasma substitute at constant flow while pressure was simultaneously recorded (6) Maximal dilatation was achieved by injections of papaverine From a level of maximal dilatation graded doses of noradrenaline were administered and steady state pressure was recorded at each dose until the maximal obtainable pressor response had been achieved Resistance curves were then plotted for each experiment and the differences within each pair concerning 1) resistance at maximal dilatation 2) steepness of the resistance curve and 3) maximal pressor response were analysed (5) Differences in these parameters indicate the presence of structural vascular changes

RESULTS

At 7 weeks of age when the SHR is considered to be in the borderline phase of hypertension urinary sodium excretion was markedly lowered compared to NCR The sodium intake was slightly lower in the hypertensive animals but this did not fully explain the difference observed in urinary sodium Faecal sodium was also analysed and higher values were consistently found in SHR compared to NCR The same pattern was seen in SHR aged 16 weeks both compared to NCR and to WKR At this age SHR is considered to be in the phase of early established hypertension To study the fate of ingested sodium fractional excretion was calc lated as percentage of the respective intakes (Fig 1) (8) These figures clearly indicate that there is a shift in excretion of sodium from the kidneys to the gastrointestinal tract in SHR both at 7 weeks and 16 weeks of age Young SHR did not show any significant sodium retention or sodium retention per gram body weight increase compared to NCR

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evident with increasing age and severity of hypertension in SHR Thus at 7 weeks of age when the blood pressure increase in SHR was only of the order of 10% only maximal pressor response was enhanced implying an increased bulk of contractile tissue of the resistance vessels At 16 weeks of age also an increased steepness of the resistance curve was evident indicating an increased wall/lumen ratio of the resistance vessels of the renal vascular bed in SHR

DISCUSSION

A consistent finding of the present study is a shift of the sodium excretion from the renal to the gastrointestinal route in SHR The increased aldosterone level in SHR could hardly contribute to this shift since this hormone is suggested to have similar effects on both sites (12) The reduced PRA values in 16 weeks old SHR indicate that the aldosterone could be mediated via central hypophyseal influencies and thus be a consequence of the increased central neuro -hormonal control in SHR (10) The increased sodium retention per gram body weight increase in SHR aged 16 weeks might in part be due to an altered growth pattern in older SHR and does not seem to contribute to the development of hypertension since it was not present in young prehypertensive SHR

The present study thus illustrates that structural vascular changes within the kidney develop progessively with the aggravation of hyper tension in SHR but that renal sodium excretion is reduced already in young prehypertensive SHR However the reduced renal ability to excrete sodium is compensated by an enhanced fecal sodium excretion so that no difference in sodium retention could be detected in the youngest animals This observed shift in sodium excretion might be caused by a primary abnormality within the gastrointestinal tract and/or of its nervous control so that less sodium is absorbed An alternative explanation is that SHR exhibit a reduced renal ability to excrete sodium already in the prehypertensive phase when structural vascular changes only partially contribute to the increased renal vascular resistance Furthermore since an increased sympathetic activity seems to greatly contribute to the development of SHR hypertension an increased sympathetic control might increase sodium reabsorbtion in SHR via a nervous control of the proximal tubular cells (3) It is therefore concluded that the observed shift in sodium balance in young SHR is not primarily due to a structurally increase in renal ascula resistance but may be due to an altered nervous control of the kidney and its vascular bed and/or of the gastrointestinal tract

patients the blood p essure in the upper half of the body had f llen to some extent d ing the follow up period and at the follow up study 6 patients had a blood pressure measured with the ordinary cuff method below 140/90 3 had p es u e betwee 140/90 and 160/95 and one had a blood p essure exceeding the last limit

The patients operated on fo aorti coarctation e compared to four dif ferent groups of either normotensive individual or hypertensi e patients studied with the same technique Sixteen patients (H) have a moderate hy-pertension (mea age 43 years) (9) Another 16 individuals are normotensive control (HC) matched to the above mentioned hypertensive indi iduals for sex age length and weight (mean age 44 years) (9) The reference material also includes 44 young men (mean ag 20 years) with mild blood pressur elevation (B; borde line group') and 29 normotensive male controls (BC) of the same age (mea age 19 years) (11) No indi idual i this study was on antihype tensive medication t the time of examination Three hypertensives had previously eceived small doses of blood p ess re lowering drugs (beta idi res rpi hyd alazine o sal retic) but all these drugs were with-d awn at l a t 24 hou s befor the tudy was done

Methods

Blood p es e at est is eco ded intraart rially through a cathet r in the ight brachial a tery (i the ef r nce groups usually i the l ft b achial a tery) Hand blood flow i eco ded pl thysmographically From the lect ically damped mean i t a t i l blood pressu e and the simult neously measured blood flow eco ded from the cathet l ed side blood flow resi tance i calcul ted Blood p ss r nd blood flow is recorded unde function l vasomot nerve blockade induced by general heating of the pa tient a well s unde maximal vasodil tation Maximal sodilatation is induced by a combination f gene l heating f the patient local heating of the hands arte ial occlusion and hand muscl work until exha tion This combination of vasodil ting timuli induces an lmost complete elaxa tion f the smooth muscl c lls i the esistance vessels of the hands (9)

Re lt

The es lts e umma ized i Fig 1 which hows i tra t i l mean blood p su at t and blood flow resistance i the hand under maximal sodi lat tion f the coa ctation group (CA) and for the 4 f ence group Mean lues fo the groups and tandard e ror f the means re p se ted It can be seen that the coa ctation group has a mea blood p e sure equalling that in the 'bo de line group (CA 93 7 and B; 93 2 mm Hg) tending to be

Hemodynamic signs indicating structural vascular changes of hypertensive type after surgery for aortic coarctation

by

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Prior to the introduction of operative treatment of aortic coarctation the prognosis of this disease was bad The patients usually died in complications to hypertension in the upper part of the body like intracranial haemhorrages rupture of major vessels or of collaterals or congestive heart failure (1) After surgery has been introduced in the treatment of these patients the prognosis has improved considerably but it has probably not been normalized since recent reports indicate a remaining elevated cardiovascular mortality in these patients (2) A number of studies also indicate a remaining slight blood pressure elevation in many of these patients in spite of a good anatomical result (2 3 4 5)

Previous studies on patients with established hypertension and borderline hypertension indicate the existence of hemodynamically important structural changes in the resistence vessels of these individuals (6 7 8 9) The aim of this study is to see whether or not structural vascular changes could be tracked in the vascular beds of a group of young men operated on for aortic coarctation about ten years previously The existence of such changes might indicate a vascular fault remaining after the previous hypertension

Material

The actual investigation is one part of a hemodynamic follow up study in patients operated on for aortic coarctation during the years 1958 1974 at the Children s Hospital in Gothenburg Of the patients operated on during this period 69 are still alive From this group 19 young symptom-free men were selected for a hemodynamic study which included among other things intraarterial blood pressures proximal and distal to the previous coarctation and cardiac output determinations The measurements were done at rest and during physical exercise The data from this study will be published separately (10) Of these patients studied hemodynamically 10 patients agreed to participate in the actual study of the peripheral hemodynamic situation The age of these 10 patients varied between 16 and 23 years (mean 21 years) The age at the operation ranged between 6 and 13 years (mean 10 years) and between 7 and 16 years (mean 11 years) had passed since the operation In all these

patients the blood pressure in the upper half of the body had fallen to some extent d ing the follow up period and at the follow up study 6 patients had a blood press r measured with the ordinary cuff method below 140/90 3 had a press re between 140/90 and 160/95 and one had a blood p essu exceeding the last limit

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Blood p es e at est is reco ded i t aart rially through a cathete i the ight brachial a tery (i the f ence groups sually i the left brachial artery) Hand blood flow is r corded pl thysmographically From the elect ically damped mea intraa t i l blood press nd the simult neously measu ed blood flow recorded from the catheterized side blood flow e istance i calcul ted Blood p ess r and blood flow is ecorded unde functional vasomot nerve blockad induced by general heating of the pa tient well s und maximal sodil t tion Maximal sodilatation is induced by a combination of gene al heating of the pati t local heating of the hand t i l oc l sion nd hand muscle work until exha stion This combination of vasodil ting timuli induce an almost compl te elaxa tion of the smooth mu l cells i the resi tanc vess ls of the hands (9)

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The esults a surma i ed i Fig 1 which shows i t aart i l me n blood p su t est nd blood flow esi tanc i the hand unde maximal vasodi l t tion fo the coa t tion group (CA) and f the 4 fe ence groups Mea lues fo the group a d standa d e ro of the means re presented It can be seen that the coa tation group has a mean blood p essu equalling that i the "borde line group" (CA 93 7 and B; 93 2 mm Hg) tending to be

higher than the pressure in one of the normotensive control groups (BC 86 9 mm Hg not significant) being significantly higher than that in the other normotensive control group (HC $p < 0$ 05) and significantly lower than the pressure in the hypertensive group (H; 122 1 mm Hg $p < 0$ 001) On the other hand blood flow resistance at maximal vasodilatation is as high in the coarctation group as in the hypertensive group (2 74 and 2 48 respectively not significant) far exceeding the resistances in the borderline group (2 02 $p < 0$ 02) and the normotensive control groups (BC 1 96 $p < 0$ 01 and HC 1 67 $p < 0$ 01) The resistance at maximal dilatation is however not increased in relation to the blood pressure in all coarctation patients In three of them there is a normal relation between resistance at maximal dilatation and resting mean blood pressure i e the same as in the reference groups

Discussion

The method used for determination of resistance at maximal dilatation in this study is mainly the same as the one previously described (9 10) but the resistance is here determined in the catheterized side instead of the non catheterized one This is true also for the reference groups It is due to the fact that the left subclavian artery is often obstructed to some extent after surgery for aortic coarctation due to technical reasons and therefore both blood pressure and blood flow has to be determined on the right side in the coarctation group The fact that blood flow is measured in the same arm as the blood pressure might influence the results to some extent since the catheter often reduces blood flow a little However since blood flow resistances used in this study for the reference groups are recalculated from the previous studies (9 10) using data from the catheterized side the error introduced by the catheter should apparently affect the different groups equally

Furthermore the method used in the coarctation group as well as in the borderline group (B) and in the corresponding normotensive control group (BC) (10) differs from the one used in the hypertensive group (H) and in its corresponding normotensive control group (HC) (9) so far that the period of indirect heat was longer in the latter groups This fact might explain the slight difference in resistance between the two normotensive groups (HC and BC)

The resting intraarterial mean blood pressure was only marginally elevated in the coarctation group and elevated to the same level as in the borderline group This is in agreement with our observations in the whole patient

material investigated with central hemodynamics (10) In that study a blood p essure elevation, mainly affecting the systolic blood press re was recorded in the right rm in most patients with a normal or low systolic press In the ight leg both at rest and du i g physical exercise A blood p essure diffe ence between the upper and lowe body half was usually found pa ticularly during exercise The observed blood pre sure elevation i the upper body half of these 10 patients is lso in agreement with the finding by othe s (2 3 4 5)

In spit of ma ginal elev tion of the mean b achial tery blood pres sure i the coarctation group blood flow esi tance at maximal vasodila t tion i consid bly inc eased The mea value for the coarctation group is of the ame mag itude as the mean value for the patients with established hype tension (H) The elev ted sistance at maximal vasodi latation indicat s that the esistance ves els i the hand and probably i the whol upper body half a e stru turally changed in the same way as the esi tance vessels of patients with stablished hypertension seem to be This is in ag eement with observations by Šamánek et l (12) It is most likely that these scul changes are secondary to the preope ative elevation of the blood p essu e in the pper half of the body The fact that the vascula changes s indicated by the high resi tance t maximal dil tation are much mo e pronounced tha should be expected from the blood press e levation may be explained by combination of a cert i blood pressu e f ll ft operation and a incomplete o lacking eve si bility of these changes This is in agreement with ou previous finding in hype tensive pati nts t eated with blood p ss e lowering drugs (13)

Thus thes results indicat that the structur l ha g of the resistance ves el of patie ts with high blood pressu e at lea t partially irre- versibl in spit of a pronounced blood p essu reduction of long d ation i young individuals F rthermo e the f ct that the vascula changes seem to be t least incompl tely ev sible is a a gument for a ea ly blood p ess e lowe ing therapy ope tive and/o pharmacological in patients with aorti coarct tion

86 9 mm Hg not significant) being significantly higher than that in the other normotensive control group (HC $p < 0.05$) and significantly lower than the pressure in the hypertensive group (H 122 1 mm Hg $p < 0.001$) On the other hand blood flow resistance at maximal vasodilatation is as high in the coarctation group as in the hypertensive group (2 74 and 2 48 respectively not significant) far exceeding the resistances in the borderline group (2 02 $p < 0.02$) and the normotensive control groups (BC; 1 96; $p < 0.01$ and HC 1 67 $p < 0.01$) The resistance at maximal dilatation is however not increased in relation to the blood pressure in all coarctation patients In three of them there is a normal relation between resistance at maximal dilatation and resting mean blood pressure i e the same as in the reference groups

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The resting intraarterial mean blood pressure was only marginally elevated in the coarctation group and elevated to the same level as in the 'borderline group This is in agreement with our observations in the whole patient

Refe ences

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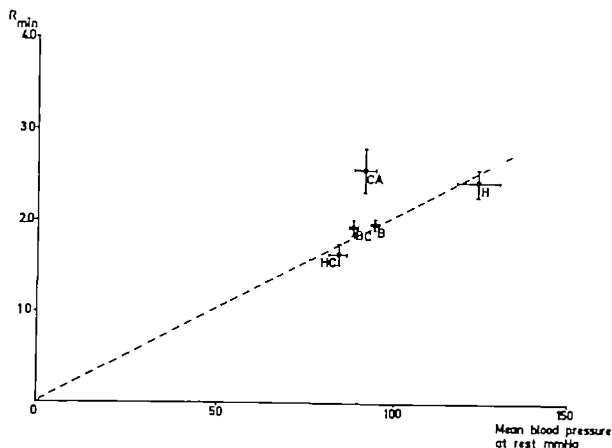


Fig 1 Intraarterial mean blood pressure at rest and blood flow resistance in the hand at maximal vasodilatation (R_{min}) in the coarctation group (CA) and in the four reference groups the hypertensive group (H) and the corresponding normotensive control group (HC) the "border line group (B) and its normotensive control group (BC) are shown Mean values for the groups and standard errors of the means are given

RESULTS

Nine of the patients had stenosis in the main stem of the renal artery 4 patients bilaterally and 5 unilaterally One of the patients with unilateral stenosis was investigated haemodynamically on the nonstenotic side His kidney has therefore been regarded as a kidney without arterial stenosis Of the remaining 8 kidneys with arterial stenosis one was due to arteriosclerosis and 7 to fibromuscular hyperplasia

Of the kidneys without arterial stenosis 3 were normal and contralateral to a hypoplastic kidney 3 comprised a normal kidney to a normal kidney One was a hypoplastic kidney and two kidneys had small areas of cortical reduction

Blood pressure

MAP before induction of the block in the group with renal artery stenosis was 136 ± 18 (S D) and after the block 126 ± 22 (S D) mmHg In the group without stenosis the MAP changed from 102 ± 16 (S D) to 91 ± 19 (S D) mmHg

Renal blood flow

In the kidneys without arterial stenosis a negative linear correlation was found between MAP and flow (r=0 77; p < 0 01) before the splanchnic block In kidneys with arterial stenosis there was no significant correlation After the block no correlation was found in either group Before the splanchnic block the percentual proportion of the total blood flow in compartment 1 was linearly correlated to the MAP This was true both for kidneys with arterial stenosis (r=0 87; p <0 01) and for those without (r=0 87; p < 0 01) Thus at a high arterial pressure compartment 1 constitued a smaller proportion of the blood flow than at a lower pressure After the block there was no significant correlation

Renal va cular re istance

A positive linear correlation was found between renal vascular resistance and mean arterial pressure in both groups The

THE EFFECT OF SPLANCHNIC BLOCK ON RENAL HAEMODYNAMICS AND RENIN PRODUCTION IN HYPERTENSIVE PATIENTS

C Mørlin L -E Lörelius P -O Löfroth L Wide L Wiklund & H Åberg

From the Departments of Internal Medicine Diagnostic Radiology Clinical Chemistry and Anaesthesiology University Hospital Uppsala Sweden

INTRODUCTION

The secretion of renin in the kidney is regulated by three different but more or less interactive mechanisms namely the sympathetic nervous system the renal baroreceptors and the sodium concentration in the macula densa (1) In an attempt to be able to better define the indications for surgical therapy in patients with renal artery stenosis the role of the sympathetic nervous system was evaluated by studying the effect of splanchnic block on the secretion of renin and on renal haemodynamics The investigation was carried out in connection with nephroangiography

PATIENTS AND METHODS

Eighteen patients - 4 men and 14 women of ages 21 - 63 years with hypertension of suspected renovascular origin were studied The patients were strictly requested not to take any antihypertensive drug during the four weeks preceeding the investigation The patients attended the hospital one week before the investigation and the last five days preceeding the examination they were given a low sodium diet (approximately 20 mmol Na^+/day) and 40 mg furosemide (Lasix^R) daily

On the day before the examination a polyethylene catheter was inserted into the patients back until its tip lay close to the splanchnic nerves at the level of the anterior margin of the first lumbar vertebra

On the day of investigation a catheter was inserted through the femoral artery for renal angiography and renal blood flow determination by the Xenon - 133 wash-out method (4 5) Blood samples were collected from both renal veins for subsequent analysis of the plasma renin activity The mean arterial pressure (MAP) was intermittently recorded proximal to the stenosis if such existed The splanchnic block was then induced with 40 ml 0 25% plain bupivacaine (Marcaine) injected via the catheter inserted on the previous day After the splanchnic block renal blood flow determination and blood sampling from

and this may indicate that compartment 1 is a distribution volume whose size is dependent on the sympathetic tone It has been shown that a decrease in blood pressure leads to an increase of PRA (3) This rise in PRA could be due to a stimulated sympathetic activity or due to baroreceptor function In our study where the sympathetic activity was eliminated by splanchnic block a decrease of the MAP and PRA was obtained Furthermore a significant correlation was found between the relative change in PRA and the relative change in renal vascular resistance The splanchnic block most likely inhibits renin secretion and decreases renal vascular resistance independently This is supported by the findings of Richardson (7)

In conclusion there is no significant difference between kidneys with arterial stenosis and those without with respect to the regulation of the haemodynamics The sympathetic system is of decisive importance for the release of renin from kidneys of patients with hypertension and this system seems to dominate over the baroreceptors at the pressure levels investigated regardless of whether there is a renal artery stenosis or not

splanchnic block caused a decrease of the renal vascular resistance but there was still a positive linear correlation between renal vascular resistance and MAP

Plasma renin

Plasma renin activity (PRA) in peripheral vein after 1 hour a rest supine before and after a low sodium diet (approx 20 mmol Na/d) and stimulation with 40 mg furosemide per day changed in patients with renal artery stenosis mean PRA from 1 88 to 4 14 ug/l/h and in patients without stenosis from 1 80 to 9 10 ug/l/h For evaluating the effect of the splanchnic block on PRA value in renal venous blood the material was divided into three groups Thirteen kidneys with arterial stenosis showed a significant decrease of the PRA in renal venous blood after the block (m=19 5 to 13 7 ug/l/h; p < 0 05) and the same was found for six kidneys with parenchymal affection (m=22 7 to 12 2 ug/l/h; p < 0 05) No significant decrease of PRA was noted in normal kidneys (m=17 5 to 16 6 ug/l/h)

Renal renin secretion rate did not allow firm conclusions (6)

Renin and renal haemodynamics

Only one significant correlation was found namely between the relative change in PRA Δ PRA% and the relative change in renal vascular resistance Δ R% in kidneys with arterial stenosis

DISCUSSION

The reduction of MAP in this investigation was of the same magnitude as previously found following splanchnic block (8) In our study the splanchnic block caused a decrease of the renal vascular resistance both in patients with renal artery stenosis and those without The decrease was most pronounced in patients with high initial resistance A reduction of the relative proportion of the flow in compartment 1 has been reported earlier in patients with hypertension (2) In our investigation this correlation was also found in kidneys with arterial stenosis After the block no such correlation existed

THE EFFECT OF HYPERTENSION ON THE MECHANOCARDIOGRAPHIC AND ELECTROCARDIOGRAPHIC MEASUREMENTS.

M. Rajasalmi O Ollinki and J Takkunen Cardiovascular Division
Department of Internal Medicine University of Oulu Oulu Finland

Left ventricular hypertrophy and heart insufficiency are the most common consequencies of arterial hypertension Both of these affect the mechanocardiographic and electrocardiographic measurements (7 8) Without these pathological states an active cardiac contribution to hypertension has been proposed and its effects on systolic time intervals shown (2 4 5) This effect has been studied in the present study in connection with electrocardiographic data for to get basis for the follow up studies of a cohort of male pulp mill workers

Population and methods:

759 male workers were studied A diastolic blood pressure of 110 mmHg or more was found in 25 men that were not using any cardioactive medication They formed Group III Group I consisted of 25 randomly elected but age matched men with diastolic blood pressure of 95 mmHg or less and to Group II were designated 25 men with a diastolic blood pressure from 96 to 109 mmHg No one had any valvular heart disease or was using any cardioactive medication

Apex cardiogram heart sounds and carotid pulse curve were registered with ECG as described before (6) A separate ECG registration was made by Olli 5000 ECG Aquisition Communication and Analysis System that provide a computer analysis of conventional 12 lead ECG and also the Frank vector loops and maximal spatial voctor of QRS (3)

Blood pressure was measured with a mercury sphygmomanometer using as diastolic enpoint the disappearence of Korotkoff voices

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Results and discussion:

The blood pressure values of all men in Groups I - III were compared to data of same subjects measured 7 years before by the same examiner In the Groups II and III there was a statistically significant elevation of both systolic and diastolic blood pressures (paired t-test p 0 01) Group I was in the same range than 7 years before as well as the 133 men who had got medication for the treatment of hypertension

The differences in QS2 PEP and PEP/LVET values as well as the differences in maximal spatial vectors in each group is presented in Table I The STI values are higher in Group I and III than in Group I The difference between Group I and III is statistically significant This is in accordance with previous results from the same factory population (6) The maximal spatial vectors did not differ between the groups but there was a good correlation between left ventricular hypertrophy found by visual reading (Minnesota code 3-1 and 3-3) and the spatial QRS vector that was evidently higher in these men In group I that means men with normal blood pressure was found 8 men with ECG consistent with the criteria of left ventricular hypertrophy In Group II there was 6 and in Group III 7 men with the same electrocardiographic diagnosis This means that the visual interpretation or the use of spatial vector do not separate hypertensive patients on the basis of left ventricular hypertrophy from normal people The QRS and T vectors in the frontal plane were in the normal range among all subjects examined

The lengthening of the STI values must be interpreted to signify a lengthening of the ventricular activation and pressure generation (4 5 6) The heart needs more time to reach the diastolic pressure and to open the aortic valve and this is seen in the

prolongation of PEP These findings are in accordance with experimental and clinical studies but all investigations have not confirmed them (1 7)

Table 1 Systolic time intervals and maximal spatial QRS vectors in the subjects included in the study

		Group I	Group II	Group III
Age		51 ± 9	48 ± 8	51 ± 10
QS2 index (ms)	mean	494 4	500 7	508 5 (x
	SD	18 1	27 8	32 4
PEP index (ms)	mean	113 1	120 2	130 1 (x
	SD	20 2	31 2	27 7
PEP/LVET	mean	0 328	0 362	0 406 (x
	SD	0 078	0 125	0 134
Maximal E QRS (μV) :				
With LVH	mean	2294	2454	1862
	SD	199	212	634
Without LVH	mean	1548	1378	1526
	SD	255	274	239

(x $p < 0$ 01 between Group I and Group III

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HDL-cholesterol in antihypertensive treatment. The Oslo Study.

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The importance of the cholesterol fraction of the high density lipoprotein (HDL) is a new aspect in the lipid theory of atherogenesis Recent reports have shown increased coronary risk in subjects with low HDL-cholesterol values (3,6) Antihypertensive drugs have been shown to induce various untoward metabolic changes; increase in serum uric acid (7), triglycerides (1,4) glucose (8) and total cholesterol (1) in thiazide treatment and uric acid increase with beta blockers (2) A triglyceride increase has also been reported in a β 1 selective adrenergic blocker (9) Furthermore, beta blockers seem to accentuate the triglyceride and uric acid increasing effect of thiazides (5) As all these metabolic changes may represent increased coronary risk, it seemed reasonable also to study the effect of some antihypertensive drug regimens on the serum concentration of HDL-cholesterol

785 men age 40-49, with no symptoms of cardiovascular disease and with a systolic blood pressure of 150-179 mm Hg and a diastolic blood pressure below 110 mm Hg were in 1973 randomized for a controlled drug treatment study

Treatment Hydrochlorothiazide (HCTH) 50 mg daily Alpha methyldopa was added if blood pressure remained above 140/90 In case of side effects, alpha methyldopa was replaced by propranolol Generally, no advice concerning diet, smoking and weight reduction were given to any group Men with alcohol problems, those having received detailed diet instructions from other physicians and those with cardiovascular events were excluded from the material in this report

In the autumn 1977 HDL-cholesterol was analysed in fresh serum samples at the routine follow-ups The same analysis was performed in non-fasting pretreatment sera stored at - 20°C from 1973 The HDL-cholesterol values in frozen sera were about 39 per cent lower than in fresh sera, and have been used only for selection of comparable groups in the different drug regimens on pretreatment lipid values

The groupswere matched on the basis of mean and distribution values of pretreatment HDL-cholesterol The untreated control group (n=33) and the groups treated with HCTH + propranolol (n=33) and HCTH + alpha methyldopa (n=33) were also well comparable with regard to pretreatment triglycerides The group treated with HCTH alone (n=26) compared well with the others with regard to pretreatment HDL-cholesterol,but tended to have somewhat lower triglycerides

After 4 year treatment the HDL-cholesterol value was 15 per cent lower in the HCTH-propranolol group as compared to the HCTH-methyldopa group, and 19 and 20 per cent lower than in the HCTH-alone and the untreated control group,respectively

The HCTH + propranolol regimen also induced a distinct triglyceride increase and a more marked uric acid increase than the other drug regimens Total serum cholesterol did not change significantly in the various treatment groups

The low HDL-cholesterol level together with the unchanged total cholesterol implies that the sum of low density lipoprotein (LDL) and very low density lipoprotein (VLDL) cholesterol increased during treatment with thiazide combined with propranolol From a metabolic and epidemio logical point of view it is possible that the reported untoward metabolic changes by this frequently used anti hypertensive drug combination may counteract the beneficial effect of pressure lowering These observations need to be confirmed in future studies specifically designed for this purpose

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On the pathogenetic role of prostaglandins in Bartter s syndrome.

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Abstra t Two pati nts on with Bartter s syndrome and one with ev r abu f diuretics were inv tigated before and aft r indom thacin treatm nt Befor indometha in the two patients showed a imilar pattern of hypokalaemic alcalo is s ndary hyp raldo t ronism and increased urinary excretion f PGE_2 and kallikrein Aft r a f w day on p roral indomethain medi ation th hypokalaemia was ignificantly improved th plasma r nin activity and th urinary ex retion of aldo t rone PGE_2 and kallikrein were n rmalized in both patients It is con luded that the ben fi ial ffect of ind methacin cannot be u d as a proof of prostaglandin ov rproduction a th primary defect in Bartter yndrome

Recently Bartt r yndrome (BS) - a ondition of hyp kalaemic al al is hyp rald teroni m hyp rplasia of the juxtaglomerular apparatu and n rmal blood pr s ure without o dema - ha b n ciat d with ov rproduction of r nal pro taglandins and th manif tation of th condition hav b en ucces fully tr ated with ag nt inhibiting pro taglandin synth i (4 6) Con quently it wa ugg ted that pro taglandin ov rproduction wa th primary d fe t in BS

In 1973 ou group pr nt d a r port on three ca es of BS (9) two adult and on hild Sin th n on of th adult died udd nly pre umably of cardia arr t We f und it of int re t to review th remaining tw cas in a protocol with measurem nt f pro taglandin (PGE_2) and kallikrein ex r tion b fore and aft r ind m tha in tr atm nt

M t rial The patients includ our original a I and 3 (9)

C 1 53 y ar old woman Aft r th establishm nt of th diagno i of BS in 197o he wa started on triamter n 25 mg/day and pot ium upplement 9o mmol/day and advi ed to take abundant salt to h diet Y t the hypokala mia was poorly controlled

(serum potassium concentration = 1 5 - 3 o mmol/l)

Case 3 18 year old woman After the establishment of the diagnosis of BS in 1971 she was started on triamterene 15o mg/day and potassium supplement 45 mmol/day and sodium supplement 8o mmol/day In the subsequent 5 years the patient has grown 12 cm (height now 154 cm) and the body weight has increased by 12 kg

Protocol The patients were started on a metabolic diet with sodium and potassium content approximating their usual diet and they received their usual triamterene dosage (fig 1 phase I) After four days triamterene was discontinued and sodium intake was reduced to normal amounts (12o mmol in case 1 and 7o mmol in case 3) The potassium intake was unchanged (fig 1 phase II) After four days treatment with indomethacin (Confortid [R] Dumex Denmark) was started (case 1: 2oo mg/day case 3: 1oo mg/day) After 8-1o days of treatment the study was terminated The 24 hour urine production was collected throughout the study and analyzed for sodium potassium and creatinine concentration Excretion of aldosterone PGE_2 and kallikrein was measured Qualitative screening for diuretics was performed on all urine samples In the morning after 6o minutes supine rest blood samples were drawn every day in case 1 and approximately every other day in case 3 Plasma was analyzed for sodium and potassium concentrations and renin activity (PRA) Every morning before breakfast the patients were weighed and blood pressure was measured

Methods PRA was measured by radio-immuno assay with the NEN angiotensin I ^{125}I kit normal range o 7 - 2 9 ng/h x ml Aldosterone excretion rate (AER) was measured by radio-immuno assay with the CIS ^{3}H - aldosterone kit normal range 8-37 µg/24h PGE_2 was measured by the method of Christensen and Leyssac (2) The range of PGE_2 excretion in 6 healthy individuals on liberal salt intake was 189 - 293 µg/24 h Kallikrein excretion was determined by a combination of the method of Beaven et al (1) and Mac Farlane et al (8) The range of kallikrein excretion in six healthy individuals on liberal salt intake was 3 5 - 13 8 EU/24 h Screening for diuretics (furosemide bumetanide and chlorthalidone) in urine was performed by thin-layer chromatography

R ulty (fig 1)

Pha I, triamterene treatment Both patients demon trat d pronounc d hypokalaemic alkalo is with very high PRA value AER was elevated in case 3 and high normal in case 1 Urinary PGE_2 exor ti n was elevated in both cases whil kallikrein excretion was above c ntrol rang in case 1 and within the c ntrol rang in case 3 Plasma sodium concentration was normal in case 3 and slightly l w red in case 1 Blood pr ssure wa low n rmal in both ca es Cr atinine clearance were normal

Ph e II, di ontinuation f triamt rene, r duction of odium int ke to normal Both ca es howed a light weight los (1 kg) reduction of AER in r ase of kallikrein xcretion and largely unchanged PRA plasma sodium and plasma potassium oncentrations and PGE_2 xcretion Blood pre ure wa unchanged

Pha e III, indom thacin treatment Both case showed a rapid mall in reas in w ight (1 and 4 kg r spectively) Plasma potassium increa ed and a plat au wa not reach d within the study period PRA AER urine PGE_2 and kallikrein showed a eizabl decrea e and reached a plat au in normal range In both cas a larg reduction in sodium excretion wa een in the am p ri d Pla ma sodium oncentration was larg ly unchanged in both cas s Blood pr ur was unchanged in both case

S re ning for diureti s in urine All 24 hour urine collections in cas 1 contain d furo emid bumetanide and chlorthalid ne Th urine from a 3 wa fr of diuretics

Di u i n Th clinical and laboratory findings in our two pati nts lo ly r embl the cas of BS earli r described (4 6 8) After the demon tration of diureti in all urine sample from cas 1 it can be saf ly assumed that th pati nt b - longs t the so-called p eudo Bartter syndrom due to covert self-admini trati n of diuretic It has rec ntly be n hown th t ind methacin red c PRA and AER in normal and hypertensive human individual (3 5) both on normal salt intake and during odium r tricti n Th re p ns i as ociated with tran ient dium r t ntion and w ight incr a Then the action of indo- meth in in BS is not uniqu but n in tates of econdary hyp rald t roni m a well In th light of these two pati nt it i obvi u that the indom thacin ffect cann t be u d a a proof of pro taglandin overproduction as th primary defect in B

(serum potassium concentration = 1 5 - 3 o mmol/l)

Case 3 18 year old woman After the establishment of the diagnosis of BS in 1971 she was started on *triamterene* 15o mg/day and potassium supplement 45 mmol/day and sodium supplement 8o mmol/day In the subsequent 5 years the patient has grown 12 cm (height now 154 cm) and the body weight has increased by 12 kg

Protocol The patients were started on a metabolic diet with sodium and potassium content approximating their usual diet and they received their usual triamterene dosage (fig 1 phase I) After four days triamterene was discontinued and sodium intake was reduced to normal" amounts (12o mmol in case 1 and 7o mmol in case 3) The potassium intake was unchanged (fig 1 phase II) After four days treatment with indomethacin (Confortid R Dumex Denmark) was started (case 1: 2oo mg/day case 3: 1oo mg/day) After 8-1o days of treatment the study was terminated The 24 hour urine production was collected throughout the study and analyzed for sodium potassium and creatinine concentration Excretion of aldosterone PGE_2 and kallikrein was measured Qualitative screening for diuretics was performed on all urine samples In the morning after 6o minutes supine rest blood samples were drawn every day in case 1 and approximately every other day in case 3 Plasma was analyzed for sodium and potassium concentrations and renin activity (PRA) Every morning before breakfast the patients were weighed and blood pressure was measured

Methods PRA was measured by radio-immuno assay with the NEN *angiotensin* I ^{125}I kit normal range o 7 - 2 9 ng/h x ml Aldosterone excretion rate (AER) was measured by radio-immuno assay with the CIS ^{3}H - aldosterone kit normal range 8-37 µg/24h PGE_2 was measured by the method of Christensen and Leyssac (2) The range of PGE_2 excretion in 6 healthy individuals on liberal salt intake was 189 - 293 µg/24 h Kallikrein excretion was determined by a combination of the method of Beaven et al (1) and Mac Farlane et al (8) The range of kallikrein excretion in six healthy individuals on liberal salt intake was 3 5 - 13 8 EU/24 h Screening for diuretics (*furosemide bumetanide and* chlorthalidone) in urine was performed by thin-layer chromatography

Re ult (fig 1)

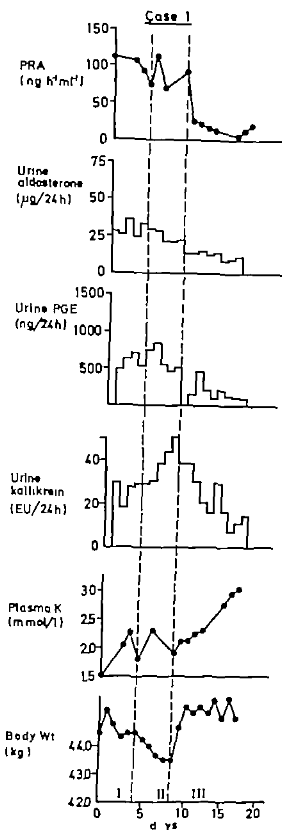
Ph e I, triamt rene treatment Both patients demon trat d pron unced hypokalaemic alkalosis with v ry high PRA values AER was el vat d in cas 3 and high normal in case 1 Urinary PGE_2 excretion was elevated in both case while kallikrein xcr tion was above control range in case 1 and within the c ntrol range in case 3 Plasma odium conc ntration was normal in case 3 and slightly lower d in case 1 Blood pressure was low n rmal in both cases Creatinine clearan e were normal

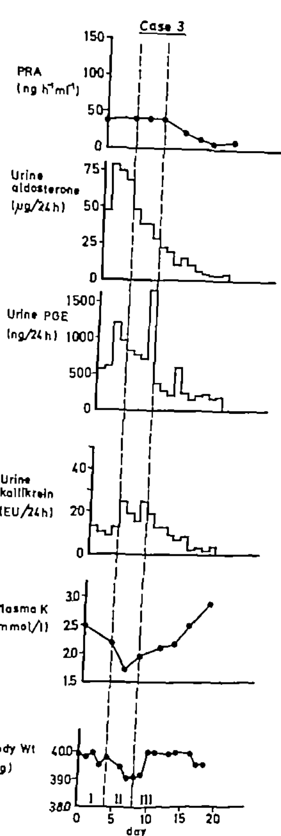
Ph se II, di continuation of triamterene, r duction of sodium int ke to n rmal Both case howed a slight weight loss (1 kg) r d ction of AER in rease of kallikrein excr tion and largely unchanged PRA plasma odium and plasma p tas ium concentrations and PGE_2 x retion Blo d pre ure was unchanged

Pha III, ind m thacin treatm nt Both cases how d a rapid mall increas in weight (1 and 2 kg r p ctively) Plasma potassium in reased and a plateau was not reached within the study period PRA AER urine PGE_2 and kallikrein showed a iz ble decr a and r ach d a plat au in normal range In both ca a large r duction in odium excretion was se n in the same p riod Plasma dium con ntration was largely unchanged in both as Blo d pr ur wa unchang d in both case

S r ning f r diureti in urine All 24 hour urin coll ction in ca e 1 contained furo emide bumetanide and chlorthalid ne Th urin from ca 3 wa fr e of diur tics

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<u>Legend to fig. 1</u>

Plasma reni ac ivi y (PRA) plasma potas ium concen-tration body weight and urinary cretion f aldo rone PGE_2 and kallikr i in th hree phas f the in- v tigation I t eatment with triamt en High sodium i ak II triamt en di tinued Normal sodium i tak III indometha in reatme t Normal sodium i ak

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TREATMENT OF HYPERTENSION WITH PRAZOSIN. AN OPEN STUDY IN GENERAL PRACTICE.

Per Fauchald M.D and Anders Helgeland M D
Hedmark Sentralsjukehus 2400 Elverum and Medical Out-Patient Clinic
Ulleval Hospital Oslo 1

In a field trial 147 general practitioners provided case reports on 1151 patients with essential hypertension treated in twelve weeks with prazosin The main purpose of the study was to evaluate the frequency of side-effects and especially the frequency of the initial reaction reported after the first dose of prazosin(1) Blood pressure, pulse rate and side-effects were registered before treatment with prazosin and after 4,8 and 12 weeks For the first four weeks prazosin was given in a fixed dose with 0 5 mg in the evening for the first two days 0 5 mg b i d for the rest of the first week, 1 mg b i d in the second week and thereafter 2 mg b i d After the control at four weeks the dose was adjusted individually with a maximum dose of 5 mg b i d

Of the 1151 patients there was 51% female and 49% male, the mean age was 59,4 years Prazosin was given as the sole antihypertensive agent in 533 patients, 246 patients were treated with prazosin and a diuretic, 162 with prazosin and a beta-blocking agent and 210 with prazosin in other combinations At the twelve weeks control the mean dose of prazosin was 4 9 mg /day in the group treated with prazosin alone and from 4 8 to 5 7 mg /day in the various groups treated with prazosin in combination with other antihypertensive agents Side-effects were mild and mostly of short duration. The treatment with prazosin was discontinued in 9 5% of the patients because of side-effects and/or unsatisfactory effect on the blood-pressure Dizziness, often of postural type was the most common side-effect (table 1) No case of typical first dose phenomenon was noted Later in the twelve week periode 7 patients(0 6%) had short-lasting

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syncopes No other serious side-effects were noted

In the group of previously untreated patients prazosin as a sole agent gave a fall in blood-pressure of 14% systolic and 13% diast

In combination with a diuretic or a betablocker we noted an addit blood-pressure reducing effect

It is concluded that with the low starting dose used in this stud the first-dose phenomenon was not seen, and that side-effects note were mostly subjective side-effects which are common in the first phase of all antihypertensive treatment

	4 weeks	8 weeks	12 weeks
Dizziness	14,9	6,4	4,2
Fatigue	9,8	5,2	2,8
Palpitations	6,0	2,2	1,9
Headache	3,9	1,9	0,9
Nausea	3,5	1,3	0,6
Syncope	0,35	0,18	0,09
Other side-effects	9,3	5,0	3,9

Table 1 Percentage of patients on treatment with side-effect

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Supplementum 626

Hypertension Control in Scandinavia

Proceedings of a Dumex symposium held in Copenhagen November 4th 5th, 1977

Edited by Bent Harvald and Kjeld Ryttig

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During these 20 years problems concerning arterial hypertension have totally changed. Effective treatment is now nearly always possible and for severe cases prognosis has radically improved. For patients who start treatment before brain, heart, or kidneys have been damaged, life-expectancy can now be considered normal or nearly normal.

Therapeutic advances have broadened the gap between negligent treatment or no treatment at all on one side and treatment according to current principles on the other. Therapeutic neglect must be considered a professional fault. It has become an obligation for the health system to ensure that society as a whole profits from the therapeutic achievements. The primary purpose is to avoid or delay complications such as stroke, myocardial infarction, or uremia. This can be achieved only by early diagnosis, qualified treatment, careful check-ups, and high patient and therapist compliance.

Related problems have been known for many years with regard to juvenile diabetes. Juvenile diabetes, however, affects less than one per cent of the population, hypertension demanding treatment affects more than 10 per cent. Juvenile diabetes generally makes itself known by characteristic symptoms, whereas early hypertension is often silent. The diagnosis of juvenile diabetes is generally clear-cut, whereas many cases of hypertension necessitate further elucidation before treatment. Average costs of treatment of juvenile diabetes are significantly lower than those of antihypertensive therapy. In diabetes both immediate and long term benefits of treatment are more easily registrable and more comprehensible than in hypertension, where patients often feel worse after starting treatment, and where increased life-expectancy is a question of statistics.

Because of high prevalence hypertension is a major challenge to the health system. Ideal screening, diagnosis, treatment, and maintenance in this single disorder would require 5-10 per cent of today's financial contribution to the entire health sector. This underlines the essential socio-medical aspects of hypertension, which have been made the subject of this symposium.

Today it is not possible to decide which organisation should be preferred to obtain ideal service at reasonable costs. The approach has been different in the Scandinavian countries, and has also differed from one center to another. Thus a considerable amount of experience has accumulated, which, however, on no earlier occasion has been presented in a collected form. It is the hope of the organizers that by offering an opportunity to exchange ideas this symposium will inspire further efforts for the benefit of the individual patients and society as a whole.

Bent Harvald

Opening Address

During these 20 years problems concerning arterial hypertension have totally changed Effective treatment is now nearly always possible and for severe cases prognosis has radically improved. For patients who start treatment before brain, heart, or kidneys have been damaged life-expectancy can now be considered normal or nearly normal

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Bent Harvald

The Value of Mass Screening for Hypertension

PETER SCHNOHR
From the Department of Medicine B, Rigshospitalet,
Copenhagen, Denmark

In a population study the Amager women study 210 randomely selected Copenhagen females aged 25-65 years were examined (10). The data collection was carried out in 1973 and the response rate was 85 per cent. Blood pressure measurements were included in the study. The systolic as well as the diastolic blood pressure rose with age. Within the five age groups, 25, 35, 45, 55 and 65 respectively 7, 16, 42, 56 and 81 per cent had a blood pressure ≥ 160 mmHg systolic and/or ≥ 95 mmHg diastolic the W.H.O. criteria for hypertension. Of these 82 women, 24 (29 per cent) knew they had high blood pressure and out of these 11 (46 per cent) received antihypertensive treatment. Three women with values below the W.H.O. criteria received antihypertensive treatment, so altogether 14 (7 per cent) of these 210 women received antihypertensive treatment.

We talk about the half of a half of a half rule (9), which we use to describe the following situation: Only half the hypertensives living in a population are aware of their condition; of these, only half are currently under treatment; and of the individuals currently under treatment, only half are receiving treatment that will adequately reduce the blood pressure levels to acceptable values. Thus only one-eighth of all hypertensives in the community have their blood pressure adequately reduced.

The findings from the Amager women study showed that only one-third of the hypertensives knew of their condition, that half of these were under treatment and that only one-fifth of these were adequately treated. Admittedly the W.H.O. criteria for hypertension are not generally agreed on as a level for medical treatment, but this study shows that a great number of hypertensives are unaware of their condition and that a high number of the treated patients are not treated adequately.

So the major problems in controlling high blood pressure are getting the symptom-free as well as hypertensives with symptoms to accept medical care, and motivating them for lifelong follow-up and probably life-long treatment.

To meet this challenge more information should be given to the public about the importance of regular blood pressure measurement and more should be done to stimulate the doctors interest in the follow-up and treatment of hypertension.

Mainly to fulfil these two purposes The Danish Heart Foundation organized a blood pressure screening campaign in supermarkets in February 1975 (11). On five consecutive afternoons some 90 medical students measured the blood pressures of 24,377 persons, 13,747 women and 10,630 men. Each person measured received a card with the BP value and an easy-to-read pamphlet about high blood pressure. Six per cent were aged 19 or less, 26% were 20-39, 43% were 40-59 and 25% were 60 years of age or more. The percentage of women and men correspond well to the total sex distribution in Copenhagen in contrast to the distribution of patients seen in general practice, where women are over-represented.

If the systolic BP exceeded the persons *age + 110* (and this sum exceeded 145) and/or the diastolic BP exceeded 100 mm-*Hg for all* ages the persons measured were advised to contact their general practitioner for further evaluation. Altogether *5,653 (23%)* persons were referred to their general practitioners. 3.7% had systolic values ≥ 200, 1.1% ≥ 220 and 0.7% ≥ 230.

Fig. 1 shows median values for systolic and diastolic BP for men and women. The

brounderségelsen or the Copenhagen City Heart Study (12). The study population is a random sample of 20,000 men and women. By the end of August 1976, approximately 3,200 had been examined and the initial response rate was 69%

Fig. 2 shows the median values for men and women and is unique because it is the first time to my knowledge that it has been found that through the entire lifespan women have lower blood pressures than men. The explanation could be that women use more antihypertensive drugs than men and at all ages visit their doctors more frequently than men. Is the latter the reason why women live longer than men?

To conclude: The major problems in controlling high blood pressure an extremely common condition which often goes undetected, untreated or inadequately treated are to get the symptom-free as well as the hypertensives with symptoms to accept medical care and to motivate them for lifelong follow-up and probably lifelong treatment.

To reach this goal we have to begin blood pressure measurement in the schools the only place passed by all persons of the community. We should stress that all doctors should include blood-pressure measurement as a routine. We should now and then perform blood-pressure screenings mainly to inform the public of the importance of the measurements, but also to detect hypertensives who would not otherwise be found. The screening should be undertaken where people are i.e. in supermarkets, at the voting polls, etc.

And finally we should have on-going prospective randomized population studies not only to describe the changes in morbidity and mortality of cardiovascular diseases, but also to serve as bases for further research. I do hope that instead of controlling hypertension only with drugs we shall also be able to control it through other ways such as weight reduction, salt restriction and more physical exercise

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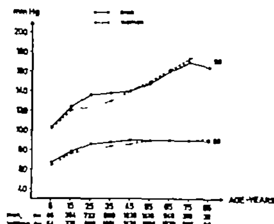


Fig. 1 Systolic and diastolic BP (*right arm*) in 13 704 men and women (median values) The supermarket campaign 1975

systolic pressure increases almost linearly with age being higher in men than in women until the forties after which age the relation becomes reverse a finding that is in agreement with the general trend in industrialized *countries (1 3 4 5 6 7 8 13)*

The cost of this screening including salary to the students (US$ 7 per hour) transportation pamphlets cards and other materials, was US$ 12,000 or US$ 0 49 per measurement Of this amount US$ 0 11 were for the BP pamphlet.

In order to assess the effect of the campaign the number of patients visiting general practitioners *during the week of the* campaign and the succeeding week were registered and compared with the corresponding number during a control week six months later (2) Forty-eight practitioners participated in the campaign period and 24 in the control week also All requests for blood-pressure measurements were included, but patients in current control were excluded Sixty per cent of the persons referred *from the supermarkets had pressures* that were still above our values for referral Twenty-three per cent of those referred had values that are generally accepted as requiring treatment These values are as follows for persons under 40 years of age a diastolic pressure above 100 mmHg for 40-49 a value above *105* for 50-59 a value above 110 and for persons 60 and over a value above 115 mmHg This means that approximately 5% of the persons screened in the supermarkets at their second blood pressure measurement had values requiring treatment. The investigation further showed that there were 2 3 *times as many visits to practitioners* for measurement of blood pressure in the *campaign period as in the control week* and the practitioners interest in blood pressure measurements was also greater during the campaign than during the control week six months later indicating that the effect declines with time. On the other hand the use of antihypertensive drugs increased significantly in Denmark the year following the campaign compared to the year before The total drug consumption has been almost stable in Denmark during the last 10 years

We felt that the main purposes of the supermarket screening, namely information about a common and health-threatening condition and finding persons with raised blood pressure were achieved It must be stated that the campaign would not have had the same response without the help of news media. Almost every Dane heard or read about BP during this particular week in February 1975

In February 1976 we began a prospective cardiovascular population study *Øster*

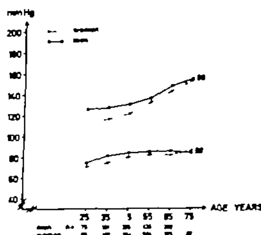


Fig 2. Systolic and diastolic BP in 3 156 men and women (median values) *The Copenhagen City Heart Study 1976*

broundersogelsen or the Copenhagen City Heart Study (12). The study population is a random sample of 20 000 men and women. By the end of August 1976, approximately 3,200 had been examined and the initial response rate was 69%.

Fig. 2 shows the median values for men and women and is unique because it is the first time to my knowledge that it has been found that through the entire lifespan women have lower blood pressures than men. The explanation could be that women use more antihypertensive drugs than men and at all ages visit their doctors more frequently than men. Is the latter the reason why women live longer than men?

To conclude: The major problems in controlling high blood pressure an extremely common condition which often goes undetected, untreated or inadequately treated are to get the symptom-free as well as the hypertensives with symptoms to accept medical care and to motivate them for lifelong follow-up and probably life long treatment.

To reach this goal we have to begin blood pressure measurement in the schools, the only place passed by all persons of the community. We should stress that all doctors should include blood-pressure measurement as a routine. We should now and then perform blood-pressure screenings mainly to inform the public of the importance f the measurements, but also to detect hypertensives who would not otherwise be found. The screening should be undertaken where people are i.e. in supermarkets, at the voting polls, etc.

And finally we should have on-going prospective randomized population studies not only to describe the changes in morbidity and mortality of cardiovascular diseases, but also to serve as bases for further research. I do hope that instead of controlling hypertension only with drugs we shall also be able to control it through other ways such as weight reduction, salt restriction and more physical exercise.

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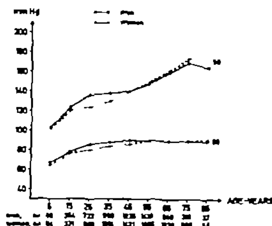


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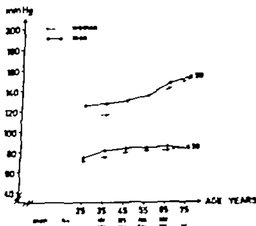


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Discussion

Berglund.

Schnohr has said that we should not start screening until we know whom we are to treat I do not believe that we know today how we should treat a 12 year old with raised blood pressure

Schnohr

If a 12 year old has organic damage I think he should be treated We have a school doctor system in Denmark which we do not fully utilize. Every year school doctors examine school children for hernia, but they never take the blood pressure

The Tromsø Heart Study
The Consequences of Blood Pressure Screening in Men Aged 20-49 Years

DAG S. THELLE and OLAV H. FØRDE
From the Institutes of Clinical and Community Medicine,
University of Tromsø, Norway

In 1974 6,593 men aged 20-49 years, i.e. 74.4% of the total population of that age in the municipality of Tromsø, Northern Norway, were examined with regard to coronary risk factors (1). Forty-eight of these subjects were reported to be on medical treatment for hypertension. Other subjects with systolic and diastolic blood pressure (BP) above certain limits were referred to six general practitioners who, on the basis of their own routine and judgement, decided if the subjects were in need of further examination or treatment (Fig. 1). The screening limits for this referral were either systolic BP equal to or above 160, 170 and 180 mmHg for age groups 20-29, 30-39 and 40-49 respectively, or diastolic BP values equal to or above 100, 105 and 110 for the same age groups. Sixty-one subjects had BP values which exceeded the limits, and 55 of them actually turned up for re-examination. Twenty-one had BP values which exceeded the systolic limits only, 22 subjects exceeded the diastolic limits only, and 12 subjects had BP values which exceeded both limits. At the re-examination by the general practitioner the subjects had diastolic blood pressure values which on average were 6.6 mmHg lower than at the screening while 7 subjects had higher readings at the re-examination.

The general practitioners found indication for medical treatment in 12 of the 55 subjects re-examined. Thirty-five were re-

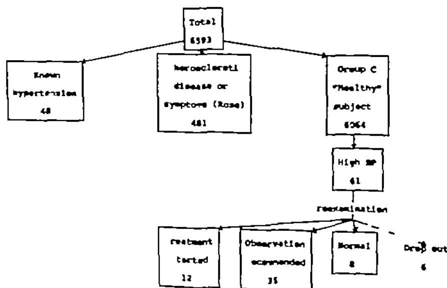


Fig. 1. Screening for hypertension in males aged 20-49 years.

Table I Results of blood pressure screening in males aged 20-49 years.

	Age groups (y)		
	20-29	30-39	40-49
Number in Group C ("Healthy") at screening	2244	2198	1622
Referral limits at screening			
Systolic	*160*	*170*	*180*
Diastolic	100	105	110
Number referred for re-examination	23	20	18
Number actually re-examined	21	16	18
"Normotensives" at re-examination			
Number	5	2	1
Systolic BP			
Screen	156 8	152 0	170
Re-ex	129 0	137 5	140
Diastolic BP			
Screen	98 0	101 0	96 0
Re-ex	77 8	92 5	85 0
"Observation" at re-examination			
Number	15	10	10
systolic BP			
Screen	148 8	163 0	174 6
Re-ex	143 3	154 0	157.5
Diastolic BP			
Screen	95.2	107 4	100 4
Re-ex	91 3	96.5	99 7
"Treatment" at re-examination			
Number	1	4	7
Systolic BP			
Screen	170	165.5	183 1
Re-ex	170	165 0	182.1
Diastolic BP			
Screen	78	111.5	117 4
Re-ex	*70*	*106.3*	115 7

commended for further observation, whereas 8 subjects were declared normotensive

Table I gives the age specific BP values for these groups at the screening and at the re-examination.

As the result of the screening the number of subjects with medically treated hypertension increased from 48 to 60. This was a surprisingly low increase. Of course we also have to consider some benefit from having placed 35 subjects on observation. On the other hand, we do not know how many of these had already been told that they had a "high" blood pressure.

Both the recall frequency and the proportion of subjects in the different age-groups who were put on medical treatment, indicate that the screening limits could have been higher for the youngest subjects and perhaps lower for the oldest. Such a change would possibly have given us a higher benefit in the form of a few more hypertensives on treatment, but would obviously also have increased the number of re-examinations.

A natural conclusion from the present study is that blood pressure screening in men aged 20-49 years gives a rather low yield, and that such a program should not be started before the age of forty

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Discussion:

Berglund.

It seems to me that Norwegians from Tromsø are like the natives of the Kalahari desert completely resistant to hypertension. Are there any other socio-economic variables and how is their sodium excretion? There is obviously a very low frequency of hypertension in Tromsø

Thelle:

There is hardly any doubt that blood pressure values in the Tromsø study are lower than those in Oslo or in the Finnmark. The subjects were summoned to a medical policlinic, where they waited for 20 to 50 minutes. They were not fasting and they were examined between 8 a.m. and 4 p.m. A few were examined at their place of work and their blood pressure was considerably higher. As for other variables, those we examined had high cholesterol and triglyceride levels, were quite heavy smokers, and took only moderate physical exercise

Beckgaard.

I collected material on 1000 hypertonics over a 40 year period. One of the things that surprised me most was that so many reached such a high age. I have divided the patients into three groups according to the diastolic pressure, namely those over 110 mmHg, those between 110 and 100 mmHg, and those under 100 mmHg. The patients are grouped according to their blood pressure at a second examination about five years after hypertension was diagnosed. All the patients had rested for half-an-hour before the blood pressure was measured. In the men in the highest group there was a relatively high death-rate from heart disease, but not especially from myocardial infarction. Oddly enough, the death-rate from myocardial infarction was highest in the group with the lowest blood pressure. The number of cases of cerebral haemorrhage was not particularly large, but was greatest in the highest blood pressure group. Even patients in the highest group reached a relatively advanced age. In the women, there was a far greater frequency of cerebral haemorrhage in the highest group though it was not particularly high in the other groups. The number of deaths from heart disease was less than in the men, in fact, the greatest number of deaths was from causes unrelated to hypertension. The women reached a considerably higher age than the men, with a strikingly large number of deaths in the late 70's.

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Re-ex	70	106 3	115 7

Threshold Values of Blood Pressure Based upon Mortality and Expected Effects of Treatment

HANS TH. WAALER
From the Health Service Research Group, Medical Research Council,
Oslo, Norway

Epidemiological studies show continuously increasing mortality with increasing blood pressure. Excess mortality is observed already at pressure levels much below average values. No clearcut thresholds are suggested by mortality figures.

A ten year follow-up of mortality of a general population (Bergen, Norway) has been used to estimate such mortality rates. Changes in life expectancy (Δe) were calculated as functions of sex, age and blood pressure (Table I). Treatment of hypertension is supposed to be able to retrieve some of these losses in years of life. This ability is assumed to be high (up to 80%) at young ages (25 years), and low (10-20%) at older ages (70 years).

Based on existing estimates of this ability which is admitted to be rather vague at present, one can calculate the potential benefit in terms of years of life as functions of sex, age and blood pressure (Table II).

To the extent that years of life are the benefit, this table should give a useful basis for setting priorities. The lower the age the higher the pressure, the higher the priority. The analysis also seems to give preference to females. The reason for this is inherent in the method as the females have a general higher longevity than males already. This is undoubtedly in contrast with the general clinical attitude. This inconsistency would, however, disappear if we excluded years of life above the age of 70.

If the figures in Table II were used for setting priorities it can be shown that 50% of the total blood pressure problem (covering all sex, age and pressure combinations with excess mortality) can be taken care of by treatment of only 4% of the individuals in the age groups 20-69 years.

Morbidity is not included in the analysis. However, the arguments above hold true as long as the morbidity is proportional to the mortality.

Actual thresholds to be applied by the physician will depend finally upon his appreciation of such figures and findings and his opinion and knowledge of side-effects of treatment plus other clinical characteristics of the patient. However, the figures presented might be a helpful indicator of where to concentrate the efforts.

Table I. Estimated loss of years of life, based upon 10 year follow-up of the population of Bergen, Norway

	Males						Females					
	Diastolic blood pressures mmHg											
Age	85	95	105	115	125	135	85	95	105	115	125	135
25	2.3	4.4	7.0	10.0	13.0	15.1	3.2	6.4	10.1	13.7	17.2	20.6
35	1.0	2.5	4.6	7.3	10.0	12.1	1.4	3.8	7.2	10.7	14.1	17.3
45		0.9	2.5	4.7	7.1	9.3	0.5	2.0	4.7	7.9	11.1	14.2
55			0.8	2.4	4.4	6.6	0.1	0.7	2.6	5.4	8.3	10.9
65				0.7	2.2	4.3			0.9	3.0	5.4	7.5

Storm Mathisen.

Bechgaard s work has given results that differ from the ones I have arrived at. The question that Bechgaard has brought up today is why does the prognosis look so promising and why do the patients in his material live so long when my young hy pertonics die so early I think it is partly because of the difference in age at the time of registration In my material hyperten sion was registered before the patients had reached 46 whereas in Bechgaard s material they were about 10 years older at the time of registration Most of the deaths in my material occurred in the age group 45 to 55 At this time of life the number of *male deaths is ten times that of the normal* population. For women it is eight times as much.

Bechgaard.

Yes, it is quite true that on the whole my patients have been older As far as I re member the average age at the time of re gistration was 46 in Storm-Mathisen s material and in mine it was 53

Screening for Hypertension in 5 249 Copenhagen Males

FINN GYNTELBERG and LONE LAURIDSEN
From the Department of Internal Medicine C, Bispebjerg Hospital,
Copenhagen, Denmark

In the autumn of 1970 a prospectively planned cardiovascular survey study was initiated on 5,249 middle-aged Copenhagen males. The main objectives of the study were to analyse:

1 Coronary risk factors in the population
2. The relationship between physical fitness and coronary risk factors.
3 The possible role of physical inactivity and poor physical fitness as coronary risk factor

All males studied were employed in public and private Copenhagen enterprises The response rate was 87.3% and the examination of all subjects comprised.

1 A short interview on the basis of a questionnaire completed beforehand.
2. Measurement of arterial blood pressure.
3 Measurement of height and weight.
4 Indirect measurement of maximal aerobic power by the bicycle ergometer test introduced by Åstrand and Ryhming.

In a random subsample of the population venous blood was drawn for determination of serum cholesterol, hemoglobin and leucocyte count. In the same subsample of 370 males a 12 lead ECG was recorded.

Among these 5,249 men, 196 men had a hitherto unknown hypertension arbitrarily defined by blood pressure values above or equal to 165 mmHg systolic and 105 mm Hg diastolic or above 110 mmHg diastolic irrespective of systolic blood pressure. These men with hitherto unknown hypertension were invited to participate in a clinical work-up in our out-patient clinic. At the beginning of the study however the clinic was not quite ready to receive the first hypertensive subjects detected by the screening and for this reason 38 men could not be included in the study These 38 men were all sent to their general practitioner for further clinical work-up Eight men refused to participate in the work-up in our out-patient clinic. Thus all together 150 men with previously undetected hypertension had a clinical examination in our out-patient clinic during the spring and summer of 1971 Ninety-six of these were given antihypertensive drugs and all were told to see their own doctor for further follow-up and control of BP The general practitioner was informed by letter about the hypertensive status.

Five years later 147 of these hypertensive patients were followed up (Table I). Three records had disappeared and could not be traced. Only 67% agreed to come for a reexamination in our out-patient clinic. Sixteen percent completed a questionnaire In

Table I Distribution of the 150 screenees according to response at the 5-year follow-up

	No. of patients	% of total
Invited to follow-up	147	98.0
Agreed to come	101	67.3
Completed questionnaire	25	16.7
No response to two letters	12	8.0
Information from priv physicians	26	17.3
No information obtainable	8	5.3
BP-values obtained	123	82.0

Table II. Estimated gains through treatment in term of years of life.

	Males						Females					
	Diastolic blood pressures mmHg											
Age	85	95	105	115	125	135	85	95	105	115	125	135
25	1.5	2.8	4 6	6.5	8 4	9 8	2.1	4.2	6 6	8 9	11.2	13 4
35	0 4	1 1	2.0	3 1	4.3	5 2	0 6	1 6	3 1	4 6	6 0	7.5
45		0 3	0 8	1 4	2.1	2.8	0.2	0 6	1 4	2 4	3 4	4.2
55			0 2	0.5	0 9	1.3		0.2	0.5	1 1	1 7	2 2
65				0 1	0.2	0 4			0 1	0 3	0.5	0 8

Discussion

Wilhelmsen.

Have the practical implications of these calculations been considered?

Waaler

A panel consisting of Storm-Mathisen, Helgeland Lund Larsen and Lund-Johansen are trying to reach a conclusion on the basis of this information. A report like the Swedish care programme will be published next year but with a slightly different approach

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3. Measurement of height and weight.
4. Indirect measurement of maximal aerobic power by the bicycle ergometer test introduced by Åstrand and Ryhming.

In a random subsample of the population venous blood was drawn for determination of serum cholesterol, hemoglobin and leucocyte count. In the same subsample of 370 males a 12 lead ECG was recorded.

Among these 5,249 men, 196 men had a hitherto unknown hypertension arbitrarily defined by blood pressure values above or equal to 165 mmHg systolic and 105 mmHg diastolic or above 110 mmHg diastolic irrespective of systolic blood pressure. These men with hitherto unknown hypertension were invited to participate in clinical work-up in our out-patient clinic. At the beginning of the study however the clinic was not quite ready to receive the first hypertensive subjects detected by the screening and for this reason 38 men could not be included in the study. These 38 men were all sent to their general practitioner for further clinical work-up. Eight men refused to participate in the work-up in our out-patient clinic. Thus all together 150 men with previously undetected hypertension had a clinical examination in our out-patient clinic during the spring and summer of 1971. Ninety-six of these were given antihypertensive drugs and all were told to see their own doctor for further follow-up and control of BP. The general practitioner was informed by letter about the hypertensive status.

Five years later 147 of these hypertensive patients were followed up (Table I). Three records had disappeared and could not be traced. Only 67% agreed to come for a re-examination in our out-patient clinic. Sixteen percent completed a questionnaire. In

Table I. Distribution of the 150 screenees according to response at the 5-year follow-up.

	No. of patients	% of total
Invited to follow-up	147	98.0
Agreed to come	101	67.3
Completed questionnaire	25	16.7
No response to two letters	12	8.0
Information from priv. physicians	26	17.3
No information obtainable	8	5.3
BP-values obtained	123	82.0

Table II. Estimated gains through treatment in term of years of life

	Males						Females					
	Diastolic blood pressures mmHg											
Age	85	95	105	115	125	135	85	95	105	115	125	135
25	1.5	2.8	4.6	6.5	8.4	9.8	2.1	4.2	6.6	8.9	11.2	13.4
35	0.4	1.1	2.0	3.1	4.3	5.2	0.6	1.6	3.1	4.6	6.0	7.5
45		0.3	0.8	1.4	2.1	2.8	0.2	0.6	1.4	2.4	3.4	4.2
55			0.2	0.5	0.9	1.3		0.2	0.5	1.1	1.7	2.2
65				0.1	0.2	0.4			0.1	0.3	0.5	0.8

Discussion.

Wilhelmsen.
Have the practical implications of these calculations been considered?

Waaler:
A panel consisting of Storm Mathisen, Helgeland Lund Larsen and Lund-Johansen are trying to reach a conclusion on the basis of this information. A report like the Swedish care programme will be published next year but with a slightly different approach

Screening for Hypertension in 5,249 Copenhagen Males

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From the Department of Internal Medicine C, Bispebjerg Hospital,
Copenhagen, Denmark

In the autumn of 1970 a prospectively planned cardiovascular survey study was initiated on 5,249 middle-aged Copenhagen males. The main objectives of the study were to analyse:

1. Coronary risk factors in the population.
2. The relationship between physical fitness and coronary risk factors.
3. The possible role of physical inactivity and poor physical fitness as a coronary risk factor.

All males studied were employed in public and private Copenhagen enterprises. The response rate was 87.3% and the examination of all subjects comprised:

1. A short interview on the basis of a questionnaire completed beforehand.
2. Measurement of arterial blood pressure.
3. Measurement of height and weight.
4. Indirect measurement of maximal aerobic power by the bicycle ergometer test introduced by Åstrand and Ryhming.

In a random subsample of the population venous blood was drawn for determination of serum cholesterol, hemoglobin and leucocyte count. In the same subsample of 370 males 12 lead ECG was recorded.

Among these 5,249 men, 196 men had a hitherto unknown hypertension arbitrarily defined by blood pressure values above or equal to 165 mmHg systolic and 105 mmHg diastolic or above 110 mmHg diastolic irrespective of systolic blood pressure. These men with hitherto unknown hypertension were invited to participate in a clinical work-up in our out-patient clinic. At the beginning of the study however the clinic was not quite ready to receive the first hypertensive subjects detected by the screening and for this reason 38 men could not be included in the study. These 38 men were all sent to their general practitioner for further clinical work-up. Eight men refused to participate in the work-up in our out-patient clinic. Thus all together 150 men with previously undetected hypertension had a clinical examination in our out-patient clinic during the spring and summer of 1971. Ninety-six of these were given antihypertensive drugs and all were told to see their own doctor for further follow-up and control of BP. The general practitioner was informed by letter about the hypertensive status.

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12 patients, who refused to participate, we could get further information from their private physicians Thus it was possible to get reasonably good information on approximately 95% of the patients initially examined Information on whether the non-responders were dead or alive could be obtained in all cases

The patients who came to the out patient clinic appeared at least twice. From all subjects venous blood samples were drawn. ECG was recorded and thoracic X-ray was taken BP was measured according to the recommendations of WHO All subjects completed a standardised questionnaire. For a diagnosis of angina pectoris the criterion of chest pain and discomfort experienced during physical activity relieved by rest and/or nitroglycerin was used

In Table II the number of deaths and cardio-vascular complications during the 5 years of observation are given Seven had died from myocardial infarction and three from cerebro-vascular accidents The

Table II Number of deaths and cardiovascular *complications*

	No of patients	% of total
Deaths	10	6 7
Non-fatal myocardial infarction	6	4 1
Cardiac decompensation	1	0 7
Angina pectoris	13	8 7
Stroke	4	2 7
Transient ischemic cerebral attack	24	16 0
Vascular surgery	2	1.3
Hospitalized in the course of hypertension	9	6 0

Causes of deaths

No of myocardial infarction	7
No of cerebro-vascular accidents	2
No of others	1

diagnosis of ischemic cerebral attack was based on a history of transient motor dysfunction of the extremities One had undergone major surgery for aortic aneurism. One patient had a leg amputated because *of femoral arterial stenosis.*

Table III Blood pressure values in treated and untreated patients on re-examination.

	Blood pressure (mmHg)	No of patients	% of total
Treated No = 94	Diastolic > 100	43	28 7
	Systolic ≥ 165	13	8 7
	Diastolic ≤ 100 and Systolic < 165	38	25.3
Untreated No = 28	Diastolic > 100	11	7.3
	Systolic ≥ 165	5	3.3
	Diastolic ≤ 100 and *Systolic < 165*	12	8 0

Table III shows that 25 3% had well controlled BP on antihypertensive medication, 8% had normal BP without treatment Thus only half a percent of the total number of the initially screened 5,249 men had benefited from the screening by having a high BP well controlled

The prognosis of the hypertensive men found by screening as to mortality and incidence of major cardio-vascular events was rather poor The mortality and number of major events were twice the expected rate. It should be taken into consideration that at the time of the screening all these men were able to work had few symptoms and were carefully instructed to have their BP controlled

It turned out however that twenty-six percent were *not controlled at all* In approximately half the hypertensives the control was not satisfactory at the time of re examination and many patients still had high BP *after 5 years The drugs* which had been prescribed for these patients were beta-blocking agents, diuretics and

methyldopa. The costs of the drug treatment were approximately US$ 100 per patient per year

The poor patient compliance and BP control in this study cannot be due to economic factors because in Denmark everybody has a private physician whom he can see free of charge and ¾ of the costs of drugs are paid for by public means.

Discussion:

Schnohr:
I do not think that Gyntelberg's material gives grounds for being negative to the screening itself The reason for the poor results was the poor follow-up The patients were not treated well enough. Probably they were not motivated for treatment well enough, either

Gyntelberg.
It is quite true that our screening was successful in so far as we did find those with raised blood pressure. However the great question is: What is the screening worth to those people who have taken part in it? I do not think we have shown that our screening has served any purpose. On the contrary it turned out much worse than we had expected. We had expected to find more people alive, fewer with complications and that the patients blood pressure had been better treated. Screening is unethical if it is not followed up with effective treatment.

Tybjærg Hansen.
Unfortunately screening is beginning to be an emotionally charged word. When a screening has not led to very much, there is no need to be miserable about it. Our supermarket screening had two purposes. Firstly to make the population aware of blood pressure. There are so many people who know nothing at all about their own physiology and we shall have to teach them. Secondly our screening was meant to show how easy it is to measure blood pressure. We must find new ways by which people can have their blood pressure measured acceptably and easily Screening is not the only way For example, doctors could organize the measurement of blood pressure by letting their nurses take it for every patient who comes for consultation. This is something that could easily be done.

Wilhelmsen.
There are a few factors that are important. a) how blood pressure is measured by screening, and b) what do we do with the patients when screening reveals hypertension? I myself am not sure what should be done Why are not patients adequately treated? The problems of hypertension should probably be approached more rationally in the population.

Principles and Experiences of a Community Control Programme for Hypertension, as Part of the North Karelia Project

P PUSKA J TUOMILEHTO A NISSINEN and J SALONEN
From the Epidemiological Research Unit
Central Public Health Laboratory of Finland, Kuopio Finland

A programme for community control of cardiovascular diseases (CVD) was established in 1972 in the county of North Karelia, a wide rural area with exceptionally high CVD mortality and morbidity and comprising some 180 000 inhabitants in Eastern Finland (1 4 5)

In the planning stage it was decided to start a comprehensive community programme, integrated with the service structure and the social organization of the community The comprehensive intervention was planned to be multifactorial and to consist of both primary and secondary prevention (3)

The main objective of the programme was defined to be a decrease of the CVD morbidity and mortality among the North Karelian population and especially among the middle-aged and male population The consideration of available epidemiological information from abroad and from Finland as well as the situation in North Karelia led to a heavy emphasis on primary prevention of the numerous disease attacks by a general reduction of the risk factors smoking serum cholesterol (i e change of diet) and high blood pressure among the population (3) The generally high level of these risk factors among the male population in the area has been shown for example, by our studies (6)

Before planning the details of the programme, background information of the problem in the community was collected a kind of "community diagnosis" was made. The community programme was designed to lead to the objectives, and the intervention was gradually implemented in a systematic way The sub-programmes were planned to contain the practical objectives and measures as well as the built-in continuous evaluation For the evaluation and management of the programme an information system was to be established which had to be reliable enough but at the same time simple enough to be practicable for application in a large community

In the comprehensive intervention the following methods have been incorporated. 1) increased health information 2) training of personnel 3) organization of services, and 4) environmental changes

One essential sub-programme is the hypertension (HT) programme (7) The main objective of the hypertension programme is to lower high blood pressures in the entire population in order to reduce the complications especially cerebral strokes and myocardial infarctions The objectives cover detection of hypertension cases adequate diagnosis treatment and follow-up of the patients At the community level this implies blood pressure measurements for the whole population systematic follow up and drug treatment of the hypertensives In order to reorganize the services special dispensaries operated by public health nurses were to be established A special regional hypertension register operating according to the WHO criteria was planned gradually to cover all the hypertensives in the community

The programme is a national pilot programme of the Finnish health authorities to test the practicability and effect of the CVD community control. The practical programme is implemented as an integrated activity within the existing health services of the County which is reinforced

by extra persons and resources to organize the activities.

The aim of the evaluation of the entire programme and the hypertension programme as part of it is to demonstrate the feasibility and the effect of the programme, as well as to estimate the costs and to obtain a comprehensive picture of the process that takes place in the programme community (3).

The methods for the evaluation and the information system for monitoring the changes in the community include, for the main objectives, a myocardial infarction and stroke register and mortality and hospital data, and for the intermediate objectives random sample surveys covering risk factors and other information. A comprehensive survey is carried out in the programme community and in a matched reference community at the beginning and at the end of the five-year programme period (baseline survey 1972, terminal survey 1977). In addition a lot of other information is collected to follow the changes in the programme area.

The baseline survey and other baseline studies were conducted in the community before starting the intervention. Among the middle-aged population (aged 25-59) the prevalence of HT (160/95) was confirmed to be high (21%). In the younger age groups the males had a higher prevalence than females and in the older groups the females had more HT than the males. About half of the hypertensives were not aware about their condition and approximately 10% of the hypertensives were under adequate treatment.

After the baseline survey the programme to control HT in the community was established and integrated with the existing service structure. Blood pressure measurements were increased in connection with the usual health services and new screening activities were introduced (6). Everybody with established high blood pressure values (160 and/or 95 in three consecutive measurements) was registered according to the protocol of the WHO HT study (7). The hypertensives were treated and followed by the local health centres. The follow-up was mostly carried out by trained nurses at the organized hypertension dispensaries with systematic health education. The patient was to see the treating physician at least once a year when the annual follow-up for the register was carried out.

During these years the feasibility of the programme has been good in the area with rather scarce medical resources. The good co-operation of the local population, community leaders and health personnel has been experienced in many ways. For example, participation rates in the surveys averaged 90 per cent.

Since the beginning of the programme blood pressure measurements gradually increased so that they covered practically the whole population. The number of registered hypertensives increased accordingly so that at the end of 1976 nearly 17,000 hypertensives were registered, which approaches 9% of the total population. Out of these subjects more than half became aware of their condition only during the programme. The frequency of control visits of those with known hypertension increased so that it led within the first years to an adequate situation for practically every known hypertensive.

An interim study showed also that the adherence to the follow-up and to the treatment was good. For example during the first year only 1% of the registered hypertensives missed their annual follow-up visit. The adherence to the treatment was then 94%.

After 4.5 years of the intervention the percentage of the middle-aged population under antihypertensive drug treatment increased among the males from 3 to 11 and among the females from 9 to 13 in the whole community. According to the register the percentage of normotensive subjects in the HT register increased during the first year from 12 to 28 and at the fourth follow-up to 38. The mean change in blood pressure during the first year was 15 mmHg reduction in the systolic and a 6 mmHg reduction in the diastolic blood pressure for those patients who had had

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Epidemiology and Treatment of Hypertension in North Karelia with Special Reference to Detection for Hypertension

JAAKKO TUOMILEHTO, PEKKA PUSKA, AULIKKI NISSINEN and JARMO VIRTAMO
From the Epidemiological Research Unit,
Central Public Health Laboratory of Finland, University of Kuopio Finland

The purpose of the baseline survey of the North Karelia Project was to measure the level of cardio-vascular risk factors. The hypertension (HT) data obtained in the baseline survey are used to evaluate the hypertension programme of the North Karelia Project by comparing them with those gathered in the terminal survey after 5-year intervention (3) On the other hand the information concerning the prevalence, detection and treatment of HT was utilized in planning the programme (2).

The survey was carried out in 1972. From the population aged 25 to 59 a 6.5 per cent random sample was drawn from the National Population Register The blood pressures of 4,275 persons (2,095 men and 2,180 women) from the representative population sample were measured. Participation rate was 90%

The level of systolic blood pressure (BP) rose with increasing age among men and women. In the age group under 45 men had a higher level than women, but the rise with age was greater among women. The same applies also to diastolic BP which however varied less.



Fig. 1 Percentage of hypertensives' according to age and sex.
Blood pressure ≥ 160/95 mmHg. Aged 30-59
≥ 150/90 mmHg. Aged 25-29



Fig. 2. Percentage of estimated need for treatment[*] for hypertension according to age and sex.
Blood pressure ≥ 175/≥ 110 or under antihypertensive drug treatment.

The casual systolic BP was over 160 mmHg in 23% of males and 31% of females. The casual diastolic BP was at least 95 mmHg in 34% of males and 36% of females. Under the age 40 more men than women were hypertensive, after the age 40 the opposite was the case (Fig. 1). The number of persons needing treatment has been estimated arbitrarily (Fig. 2)

Sixteen percent of women and 6% of men aged 45-59 used antihypertensive drugs. In the age groups under 45 there was no significant difference between the sexes. Three percent of all men and 9% of all women were under treatment. Fifteen percent of all men and 34% of all women had been informed of having elevated BP HT had been detected at a visit to a doctor in about half of the cases. During stay at a hospital or by screening, HT was detected more frequently in men than women. A public health nurse had discovered two fifths of all female hypertensive cases and the vast majority of female hypertensives aged 25-44 had been diagnosed by public health nurses. The proportion of cases diagnosed in hospital increased and that of cases detected by screening decreased with

this follow-up It must be noted that 65% of these hypertensives were already under *drug treatment at the time of the registra* tion.

The preliminary information from the stroke register shows that the annual stroke incidence rates were reduced in 1975 to 1 9 for males and 1 8 for females in the 25 74 age group calculated per 1000 inhabitants No age specific trend was noticed in this reduction which became evident during the third year of the intervention, i e. 1974 The 3 week case fatality rates of the registered strokes were reduced from 1972 to 1975 from 23% to 17% among the males and *from 27% to 10% among the females* During the same period the same system of registration showed no change in the in cidence rates of acute myocardial infarc tion (MI) In the total and MI mortality rates of middle-aged males and females during the three first years of the programme in North Karelia a reduction can be seen compared with the two pre-programme years

The presented evaluation of the programme is preliminary Only the final evaluation using different data sources and a *matched reference area will reveal the final* effect of the programme It can, however be already now stated that the feasibility of this community programme has been good and it has needed minimal amount of extra resources The interim evaluation indicates a clear improvement in the blood pressure situation of the population and it is possible that this is associated with a reduction in the occurrence of cerebral strokes in the community

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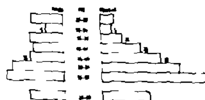


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increasing age among men The proportion of hypertensives detected under the age of 30 was greater among women than among men

About half of the men and women who were aware of HT reported having used antihypertensive drugs at one time or another (Table I) Every fifth man and every fourth woman had used antihypertensive drugs during the week preceding the examination The proportion of men using drugs was greater than that of women in the age group 25-44 whereas in the age group 45-59 women used drugs more frequently than men

Half of the men and women who had used antihypertensive drugs had been under treatment for less than two years Only one fifth of the men and one third of the women who had used drugs had been under drug treatment for more than five years Approximately one-third of the men and women who had used antihypertensive drugs had been continually under drug treatment. Half of those examined reported that there had been breaks in drug treatment. One quarter of the men and two fifths of the women had been living without drug treatment for more than five years Only very few of those who had discontinued antihypertensive drug treatment were normotensive at the moment of the examination.

A majority (60%) of those examined had had their BP checked at least once within the past six months In 5% BP had not been measured during the past five years One third of those examined reported that they had had their BP checked at regular intervals Those who had abandoned regular check-ups said that they had done so because of their doctor s instructions one tenth reported that work had obstructed regular measurements Those who had discontinued antihypertensive drug treatment said that they had followed their doctor s instructions in doing so in a few cases side effects of the drugs had caused discontinuation Every fifth man and every twentieth woman said that they had forgotten to renew the prescriptions for one reason or another

According to the criteria for HT 20% of men and 26% of women in the baseline survey were classified as hypertensives Almost half of the hypertensive men and women were aware of their condition and about half of them had been under treatment at one time or another At the time of the examination two fifths of the men and one half of the women who had been under treatment were still being treated Among the subjects who had been told about their HT drug treatment, normotension was restored in 13% of the males and 10% of the females

Table 1 Percentage of unknown untreated and inadequately treated hypertensives in North Karelia in 1972.

	males		females	
Representative population sample	2095	(100%)	2180	(100%)
Hypertensives [1] in the sample	419	(20%)	567	(26%)
Not aware of their hypertension	230/419	(55%)	301/567	(53%)
Never treated (out of those aware)	94/189	(50%)	122/266	(46%)
Not under drug treatment (out of the treated)	60/95	(60%)	72/144	(50%)
Not normotensive out of the treated	20/35	(55%)	55/72	(77%)

Blood pressure ≥ 160/ ≥ 95 aged 30-59 and
≥ 150/ ≥ 90 aged 25-29
or under antihypertensive drug treatment

Our results seem to have confirmed that the general level of BP is high in North Karelia higher than in other parts of Finland (1) The blood pressure level of men under 45 years is clearly higher than that of women. This applies both to systolic and diastolic pressures The mean BP does not rise much with age in men but the rise is steep in women.

The prevalence of HT is 20% among men and 26% among women. Also here the clear age specific differences are seen This means that the management of HT in the community should cover men at an earlier age than women. Furthermore middle-aged men run a much higher risk of cardiovascular diseases. This higher risk can partly be referred to a higher BP level in younger age groups. However our findings concerning treatment of HT are not very promising In 1972, before the intervention of the North Karelia Project more women were under treatment and there was no difference between sexes in younger age groups. Thus the treatment of young men has definitely been inadequate

To provide long-term treatment for HT in North Karelia has been as problematic as everywhere else in the world (4) The main problem seems to be that treatment is discontinued in most cases within one or two years The reason is to be found in our health care system, especially in doctors who have not been very active in keeping patients on a long-term treatment and follow-up

According to our experiences measurement of BP was carried out on a wide scale already before special intervention. In North Karelia before the intervention most cases were detected by a doctor's examination and rather many in a hospital. This was true especially for men. In women the follow-up of the hypertensive cases has apparently been more successful because of the active role of public health nurses. High BP has been found in women earlier than in men in spite of the fact that the BP level in men is higher in the younger age groups.

Our results show that even in women the effect of all measures in the management of HT has been unsatisfactory What is needed is primarily a systematic way to organize the follow-up and treatment services, but also services for early detection of HT especially in young men.

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Discussion:

Posborg Petersen:

Do you have any suggestions or knowledge of factors which might be responsible for the very high frequency of hypertension in the North Karelia district? Compared with the study from Tromsø the frequency is ten to twenty times as high. Dull, who studied the frequency of hypertension in some Japanese island, could demonstrate that there was a clear association between high salt intake and high frequency of hypertension Do you have any suggestions as to such factors, and is the frequency of hypertension the only factor responsible for the high incidence of cardiovascular disease in North Karelia?

Tuomilehto.

W have studied possible background factors for essential hypertension in North Karelia. We hav used such variables as body weight, physical exercise and some socio-economic factors. We found that there was a clear association between hypertension and socio-economic factors such as family income and education. There was also an association with body weight but all these factors could explain only about twenty per cent of the variation

of blood pressure. We have not done any studies until now about salt consumption but during our terminal survey we are going to study this question on the basis of urinary salt excretion. Karvonen and Keys in their sample study in Finland found that salt consumption in eastern Finland is rather high

Puska
High cardiovascular risk in North Karelia from our prospective studies seem to depend on three factors serum cholesterol, smoking, and high blood pressure The North Karelian population has the highest known combined level of these risk factors Especially serum cholesterol level is high. As far as hypertension is concerned there are some other populations of similar levels and smoking habits in North Karelia are not exceptional

Follow up of the Hypertensive Patients in North Karelia and some Results from the Hypertension Register

AULIKKI NISSINEN, JAAKKO TUOMILEHTO and PEKKA PUSKA
From the Epidemiological Research Unit,
Central Public Health Laboratory of Finland, University of Kuopio, Finland

Since its establishment in 1972 the North Karelia Project has continually followed all hypertensive patients in the whole community through a hypertension (HT) register (4, 8). Once having entered the register the patients have had an annual examination. In 1977 the number of patients on the register was 17 115. The criteria for HT have been: 150 and/or 95 mmHg (-29 years), 160 and/or 95 mmHg (30-64 years), 170 and/or 95 mmHg (65- years), or already receiving drug treatment for hypertension.

The main goal of this register has been to maintain patients in treatment (3) and to get information about the progress of the HT programme. However, the final evaluation of the programme as part of the project will be made by using the terminal survey (1).

Here we describe the progress of the treatment and its effect on blood pressure (BP) of registered patients during the first four years of the register.

Out of the 16,967 registered patients 6,307 were males and 10 661 females. About 60% of these men and 40% of the women were under 55. 16% of males and 30% of females registered were over 65. Among registered patients 77% have been followed for more than one year, 63% for more than two years, 42% for more than three years and 15% for more than four years.

The majority of patients have been referred to the register as known HT cases and half of the patients were aware of their HT before the establishment of the North Karelia Project in 1972 (Table I).

Half of the registrants had previously been or were still under drug treatment. Eighteen percent have been identified by mass screening. At the initial examination 98% of the patients in the register were

Table I. Time of awareness of high blood pressure on entering the hypertension register

	Time of awareness of high blood pressure	The registration year 1972 (%)	1973 (%)	1974 (%)	1975 (%)	1976-April 1977 (%)	Total (%)
	1971 or before	81	57	38	34	32	49
I ntervention	1972	19	18	10	9	8	13
	1973		25	19	13	10	16
	1974			34	20	9	13
	1975				24	14	6
	1976- April 1977					28	3
	Total	100	100	100	100	100	100
	Number	2684	5296	4371	2835	1751	16937

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Table II Proportion of registered patients under antihypertensive drug treatment in the initial and annual follow-up examinations, by sex

Time of examination	males (%)	females (%)	total (%)
Initial examination	51	59	56
1 Annual follow-up	68	75	73
2 Annual follow up	75	79	77
3 Annual follow-up	80	86	84
4 Annual follow up	80	88	86

diagnosed as essential hypertensives and only in 1% a certain cause for secondary HT was found

Local general practitioners have been responsible for the treatment. Each health centre has established an HT dispensary which is managed by a public health nurse Patients visit the nurse about 3-6 times and the doctor about 1 2 times per year The doctor and the nurse have a close co-operation so that the nurse can consult the doctor whenever necessary

Registration of patients was decided by a doctor after three consecutive BP measurements Doctors have filled in the initial record forms The registration of patients has been continual from 1972 to spring 1977 The coordination centre of the North Karelia Project asked the patients two months before the annual follow up date to visit their doctor The aim of this procedure was to avoid drop-outs and to make it possible for the patient to combine other medical problems with the annual follow up visit With this method it has been possible to get information on about 90% of all the patients in the register in each follow-up year

A doctor personally or a qualified assistant has measured BP s for the register data according to the recommendation of the North Karelia Project This requires measurement after 5 10 minutes rest in a sitting position The diastolic BP was recorded as the fifth phase of Korotkoff's sounds

During the first follow up year 44% of the registered patients had their BP measured more than 7 times by either a doctor or a public health nurse Later on the frequency of the measurement decreased

The proportion of patients under treatment has increased during the follow-up period so that after 3 years follow up 84%

Table III Percentage of normotensives in annual follow-up examinations according to different criteria.

Time of examination	The criteria of hypertension (mmHg) A) (%)	DBP < 100 (%)	DBP < 105 (%)	SBP < 160 (%)
Initial examination	12	54	62	34
1 Follow-up	28	72	80	53
2. Follow-up	33	77	85	57
3 Follow-up	36	80	88	56
4 Follow-up	38	83	89	54

A) ≤ 29 years < 150/90
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≥ 65 years < 170/95

were under drug treatment (Table II). The average BP of the patients decreased during all the follow-up years being most marked during the first year (Fig. 1) Proportion of the normotensive patients in the annual follow-up examinations increased clearly the year after the first follow-up year (Table III).

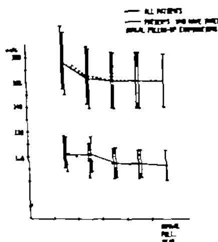


Fig 1 Changes of the average BP in all registered patients and in patients with three annual follow up examinations.

The first annual follow-up was missed in 13% of the cases. Approximately one-third was due to death, emigration, etc. In the second annual follow-up this percentage was 10, in the third 5 and in the fourth 1

The 17 115 patients in the register constitute 9 7% of the total population of North Karelia. The proportion of males in the register has continually increased and now the proportion of males and females is as expected. This shows that the register has succeeded in covering also the middle aged males who have especially high CVD risk.

Practically all hypertensives in North Karelia are today aware of their HT and most of them are also registered. Half of the patients having entered the register have become aware of their HT during the 5-year intervention period of the North Karelia Project.

The establishment of the register has been feasible owing to very active co-operation with general practitioners and public health nurses in the health centres. Registration of the patients as well as the follow up have been performed by them The follow-up has been successful, the number of drop-outs has been small. More than half the drop-outs in the follow-up has been due to some known reason like death or emigration (5) This good patient compliance can be ascribed to the HT dispensary system run by public health nurses

A great proportion of the patients in the register have become normotensive. The continuous decrease in average BP is a sign that the treatment is becoming more and more adequate. It must be remembered that even partial decrease of high BP reduces the risk of serious cardiovascular complications (2, 6, 7)

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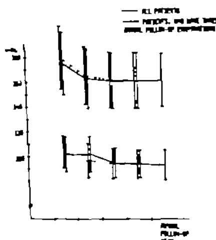


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Discussion.

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The public health nurses have done most of the check up visits and the results show what public health nurses can do The efforts of the doctors were more or less the same as before our intervention.

Leren.
Which drugs did you use and did the nurses have the right to prescribe antihypertensives?

Tuomilehto
In Finland we have approximately 40 different antihypertensive drugs and I would guess that almost all of them have been used About 70% of those treated get some kind of diuretic, about 50% some kind of beta blocker and some 30% methyldopa.

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The doctors prescribe the drugs but the nurses can regulate the treatment in close contact with the doctor It is up to the local doctors to decide when to start the drug treatment.

Coronary Risk and Socio-economic Status, The Oslo Study

P LEREN, A. HELGELAND L. HJERMANN I HOLME, and P.G. LUND-LARSEN
From the Medical Out-Patient Clinic and Life Insurance Companies' Institute for Medical Statistics, Ulleval Hospital, Oslo Norway

In the Oslo Study 18,000 men, aged 20-49 had a health examination This examination, the screening phase, lasted from May 1972 to December 1973 The screening data were then matched with the 1970 census and the 1972 income data. The census data included information about the educational level of the participating men

Detailed reports have earlier been published (1 2, 3).

This presentation deals with 14,677 men aged 40-49 without known cardiovascular disease.

Blood pressure was independent of income. Increasing educational level, how ever was associated with decreasing blood pressure. When the men were divided into five social classes taking into account both income and education certain characteristics proved to be dependent on the socio-economic level of the men.

Blood pressure showed a slight increase with decreasing socio-economic status. Serum cholesterol and percentage of daily smokers showed a marked and systematic increase from the highest to the lowest social class. Thus, the total coronary risk (risk score) based on systolic blood pressure, serum cholesterol and number of cigarettes increased from 5 7 in the highest social class to 13.3 in the lowest.

The study also revealed that various occupations were associated with different coronary risk The four highest risk occupations were taxi drivers, construction workers and navvies, longshoremen and ship officers. The highest systolic pressure was measured in metal foundry workers (140.8 mmHg) and the highest diastolic in ship s officers (82.2 mmHg)

The four lowest risk occupations were religious workers, physicians lawyers and headmasters. The latter had both the lowest systolic and diastolic pressure (127 0/82.2 mmHg) Owing to small numbers in each occupational group a possible selection effect must be considered.

Dividing social class III into three subgroups, those with high income and low education (over-achievers) those with both medium income and education (medium-achievers) and those with low income and high education (under-achievers), a great variance in coronary risk emerged. Blood pressure and serum cholesterol showed significantly lower levels in the under-achievers, as compared with the over achievers, and although cigarette smoking was very much the same, the total coronary risk rose from 8.2 in the under-achievers to 12.1 in the over-achievers

Thus, coronary heart disease risk as judged from systolic blood pressure, serum cholesterol and number of cigarettes, seems to be linked to socio-economic status. Those with the highest educational and economic status are better off

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Extra follow-up visits:	Nkr	72,000
Additional laboratory analyses:	Nkr	88,000
Income loss (2 working hours per visit):	Nkr	144,000
Antihypertensive drugs:	Nkr	860,000
	Nkr	1164,000

Additional cost per patient per year: Nkr 730

If the treatment cut off point is reduced from diast. 110 to 100 mmHg, additional 40-50,000 Norwegians will have to be treated with antihypertensive drugs (7). Thus an uncertain health gain will cost another 36 million Nkr per year compared to a non-drug regimen with systematic follow-up. This calculation does not include the cost of possible side effects of the drug.

2. The side-effects of the drugs observed in this trial are about the same as seen in other studies. We have also looked for possible effects of thiazides on serum lipids. In the total group treated with thiazides there was no significant increase in serum triglycerides and cholesterol was unchanged. In those who experienced the greatest increase in uric acid during thiazide treatment, there was a significant increase in triglycerides. Cholesterol was unchanged. Increase in body weight during thiazide treatment seems to induce a significantly greater increase in serum uric acid and triglycerides than corresponding weight increase in the control group (2).

3. *The drop-out problem* in the treatment of mild hypertension seems to vary in different populations, and with different ways of managing the follow-up examinations (1 4). In this study the patients have seen the same physician and the same paramedical staff during 4 years and the drop-out rate has been small, 0.6 per cent, and the same in both groups, (Table I).

4. Does drug regimen lead to more mental anxiety than a non-drug observation routine?

Table II shows preliminary results from a

Table I. Oslo Study. Drop-outs from hypertension trial.

Total number of observed patients in the treatment and control group 4 years observation.	785
Drop-out rate	0.6 per cent
Treatment group	2 patients
Control group	3 patients

questionnaire mailed to both groups. Only few patients equal in both groups, reported that the procedure had promoted a feeling of anxiety.

Only about 10 per cent of the patients would have preferred the follow-up to have taken place in their private physician s surgery.

Table II. Oslo Study. Condition of patients.

Regimen	Feeling of anxiety	Feeling of safety	Indifferent
Drug treatment (n = 80)	2.5%	80%	17.5%
No drug treatment and follow-up visits (n = 100)	1%	86%	13%

The blood pressure difference between the two regimens is 17 mmHg systolic and about 10 mmHg diastolic. About 8 per cent of the control group have passed the "ethical roof" with blood pressure above 180/110 mmHg (mean of the two lowest readings of 3 visits 3 weeks apart). These patients have been offered treatment. Reports of cardiovascular events will be presented in 1979 when all patients have been in the trial for at least 5 years.

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Mild Hypertension - Early Drug Treatment or Follow-up only? The Oslo Study

A. HELGELAND I BAKSAAS AASEN and P LEREN
From the Medical Out Patient Clinic and Division of Clinical Pharmacology and Toxicology Central Laboratory Ullevaal Hospital, Oslo Norway

The 1970 Veterans Administration report of drug treatment of mild and moderate hypertension (diastolic BP 90-114 mmHg) aroused great interest in hypertension treatment (5) Later reports from the same centre have shown fewer benefits from drug treatment of milder hypertension (diastolic BP 90-104 mmHg) unless the patients had cardiovascular complications at entry or were above 50 years of age (6) It seems that persons with mild hypertension without complications are at a lower risk and possible benefits from drug treatment should be weighed against the inconvenience side effects and cost of drug treatment. From their controlled trial of drug treatment of mild hypertension in 400 patients for 10 years McFate Smith et al. conclude that a non-drug regimen with systematic follow-up may be a useful alternative to drug treatment (3)

The hypertension trial in the Oslo Study started in 1973 with 406 men in the drug group and 379 men in a non-treated control group (no placebo) Age at start was 40-49 and blood pressure range was 150-179 mmHg systolic, and below 110 mmHg diastolic. Sample size is small and a 5 year follow up study might not be conclusive with regard to "hard" events such as death myocardial infarction and cerebrovascular accidents Additional information might be gained by exercise tests at start and at 5-year follow-up Another aim is to gain practical experience with the management of symptom-free hypertensives and to elucidate side effects of the antihypertensive drugs.

Some experiences from 4-year follow up will be discussed

1 Additional cost of drug regimen compared with a non-drug management with systematic follow-up

The calculations were based on experiences from pretreatment examinations average drug doses and other follow-up results Analyses made for pure, scientific reasons have been omitted

The drug regimen. Hydrochlorothiazide 50 mg per day If blood pressure remains above 140/90 mmHg, alpha-methyldopa has been added In case of side effects alpha methyldopa has been replaced by propranolol At 4-year follow-up the distribution of the drugs was Hydrochlorothiazide (HCTH) alone· 190 patients HCTH + alpha-methyldopa. 89 HCTH + propranolol 92 other drugs 33 Two patients refused to take drugs

Pretreatment evaluation was the same in both groups

After start the treated patients had 4 follow-up visits the first year later 2 visits each year The control patients have been seen once a year

Laboratory tests Serum potassium and uric acid have been done after 3 months in the treatment group later once a year fasting blood glucose after 3 years These analyses have not been undertaken in the control group All other tests have been equal for the two groups

Additional costs in the treatment group compared with the controls during 4 years (400 patients)·

Extra follow-up visits:	Nkr	72,000
Additional laboratory analyses:	Nkr	88,000
Income loss (2 working hours per visit):	Nkr	144,000
Antihypertensive drugs	Nkr	860,000
	Nkr	1164,000

Additional cost per patient per year Nkr 730

If the treatment cut off point is reduced from diast. 110 to 100 mmHg, additional 40-50,000 Norwegians will have to be treated with antihypertensive drugs (7). Thus an uncertain health gain will cost another 36 million Nkr per year compared to a non-drug regimen with systematic follow-up. This calculation does not include the cost of possible side effects of the drug.

2. The side-effects of the drugs observed in this trial are about the same as seen in other studies. We have also looked for possible effects of thiazides on serum lipids. In the total group treated with thiazides there was no significant increase in serum triglycerides, and cholesterol was unchanged. In those who experienced the greatest increase in uric acid during thiazide treatment, there was a significant increase in triglycerides. Cholesterol was unchanged. Increase in body weight during thiazide treatment seems to induce a significantly greater increase in serum uric acid and triglycerides than corresponding weight increase in the control group (2)

3. The drop-out problem in the treatment of mild hypertension seems to vary in different populations, and with different ways of managing the follow-up examinations (1 4). In this study the patients have seen the same physician and the same paramedical staff during 4 years and the drop-out rate has been small, 0.6 per cent, and the same in both groups, (Table I).

4. Does a drug regimen lead to more mental anxiety than a non-drug observation routine?

Table II shows preliminary results from a questionnaire mailed to both groups. Only few patients, equal in both groups, reported that the procedure had promoted a feeling of anxiety

Only about 10 per cent of the patients would have preferred the follow-up to have taken place in their private physician s surgery

Table I Oslo Study Drop-outs from hypertension trial.

Total number of observed patients in the treatment and control group 4 years observation	785
Drop-out rate	0 6 per cent
Treatment group	2 patients
Control group	3 patients

Table II Oslo Study Condition of patients.

Regimen	Feeling of anxiety	Feeling of safety	Indifferent
Drug treatment (n = 80)	2.5%	80%	17.5%
No drug treatment and follow-up visits (n = 100)	1%	86%	13%

The blood pressure difference between the two regimens is 17 mmHg systolic and about 10 mmHg diastolic. About 8 per cent of the control group have passed the "ethical roof" with blood pressure above 180/110 mmHg (mean of the two lowest readings of 3 visits 3 weeks apart). These patients have been offered treatment. Reports of cardiovascular events will be presented in 1979 when all patients have been in the trial for at least 5 years.

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Mild Hypertension - Early Drug Treatment or Follow-up only? The Oslo Study

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From the Medical Out Patient Clinic and Division of Clinical Pharmacology and Toxicology Central Laboratory Ulleval Hospital, Oslo Norway

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Additional costs in the treatment group compared with the controls during 4 years (400 patients)

Prevalence of Hypertension in the Glostrup Population Studies

LEIF HAGERUP, MARIANNE SCHROLL, MARIE ERIKSEN, HANNE HOLLNAGEL, and ERIK AGNER
From the Section of Prospective Medicine, Medical Department C, Glostrup County Hospital, Copenhagen, Denmark

The Glostrup population studies are prospective studies of 40, 50, 60, 70 and 80 year old men and women.

From the communities surrounding Glostrup Hospital the total populations from each decade have been invited to an examination. Each separate survey was primarily aimed at investigating the prevalence of cardiovascular risk factors. The surveys of the 60 and 80 year old people furthermore serve as incidence studies as they are re-examinations of the 50 and 70 year old populations previously studied.

The examination program included questionnaires, physical examination, chest X-ray, ECG at rest and during exercise and blood samples, according to criteria of WHO.

The blood pressure was measured after 10 minutes rest in the supine position with a standard cuff and a mercury manometer. The diastolic blood pressure was measured at the disappearance of the Korotkoff sounds (phase V).

Table I. Systolic BP ± sd/Diastolic BP ± sd in men

40 years old.	125 ± 17 / 81 ± 11	(= 500)
50 years old:	137 ± 19 / 87 ± 13	(n = 431)
60 years old.	138 ± 22 / 87 ± 13	(n = 359)
70 years old.	153 ± 23 / 86 ± 13	(n = 223)
80 years old.	137 ± 22 / 71 ± 13	(n = 99)

Table II. Systolic BP sd/Diastolic BP ± sd in women

40 years old	118 ± 15 / 75 ± 10	(n = 528)
50 years old·	141 ± 22 / 87 ± 13	(n = 355)
60 years old.	140 ± 24 / 86 ± 14	(n = 306)
70 years old.	157 ± 28 / 82 ± 13	(n = 206)
80 years old.	147 ± 26 / 70 ± 12	(n = 130)

Tables I and II show as in other studies increasing systolic blood pressure with age, especially in women past 50.

Frequency of treatment with antihypertensive drugs varied from 0.3% of the 50 year old population to 6.8% of the 60 year old, whereas diuretics were used by 1.5% of the 50 year old, by 11.6% of the 80 year old men, and by 40% of the 80 year old women.

A great part of those treated did not achieve sufficient lowering of the blood pressure, which means that the found prevalence figures are not far from real values.

Using limits proposed by WHO for hypertension (systolic BP ≥ 160 and diastolic BP ≥ 95) treatment will be needed in the proportion of each age group shown in table III.

Table III. Proportion of each age group needing antihypertensive therapy

	Men	Women
40 year old:	11/500 = 2.2%	8/528 = 1.5%
50 year old:	45/436 = 10%	51/360 = 14%
60 year old:	40/359 = 11%	37/306 = 12%
70 year old.	50/223 = 22%	35/206 = 17%
80 year old.	4/99 = 4%	4/130 = 3%

In the 10 year follow-up of the original 50 year old population it was found that the incidence of cardiovascular diseases was related to increasing diastolic blood pressure and especially to diastolic pressures over 100 mmHg. Though the blood pressure was only measured on one occasion it seemed to be a good predictor of future risk.

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Discussion:

Agner

How has the blood pressure development been in the untreated control group?

And, furthermore, has there ever been a proper investigation on what happens to high blood pressure when the medicine is discontinued?

Helgeland

In our untreated control group the mean blood pressure level is surprisingly steady from year to year, but in about [illegible]-20 per cent of the patients there seems to take place a distinct increase in blood pressure.

Bechgaard

I have also felt that this is a very important question and one which I have considered during my long-term observations. My impression is that of course the mean group lies at a certain level, but there are many exceptions. For inexplicable reasons, some regain their normal blood pressure, or at any rate a lower blood pressure, but it is quite certain that the same level can be maintained without rising for many years. However, a slight increase during the years is most common.

Hans Ibsen

In the Veterans Administration study there was an observation period of about 4 years for both the placebo group and the treatment group. In the placebo group, there were quite a few whose diastolic blood pressure rose during that period and who definitely needed treatment. The active treatment was discontinued in a large number. A month or two might pass, but at some time after withdrawal the blood pressure rose in most of the patients to levels again requiring hypertensive treatment.

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Cardiovascular Manifestations and Changes in Blood Pressure from the Age of 50 to the Age of 60, in the Glostrup Population of Men and Women Born in 1914

MARIANNE SCHROLL
From the Section of Prospective Medicine, Medical Dept. C,
Glostrup County Hospital, Copenhagen, Denmark

In 1964 a total population of 514 men and 461 women, living in seven municipalities around Glostrup County Hospital, was invited for a health examination with special emphasis on risk factors for coronary heart disease. Eighty-two per cent of the 975 proposita participated in the baseline-examination. After a ten year interval the 790 survivors were invited for a follow-up examination in which 666 participated. On both occasions blood pressure was measured several times. For comparison we used the 10 o clock supine blood pressure taken after 10 minutes' rest (using Korotkoff phase V as diastolic blood pressure).

No statistically significant difference was found between the distribution curves of systolic or diastolic blood pressure measured at the age of fifty and the age of sixty (1). This does not imply that the incidence of hypertension was zero. In this survey hypertensives had a considerable mortality. Antihypertensive drugs lowered the blood pressure in some of the participants treated by their general practitioners. Non-participants and participants in the re-examination did not differ in entry blood pressure values. Some participants must then have developed hypertension over the decade. It is of some importance to know if it was the borderline-hypertensives who developed manifest hypertension.

The target population was the participants who had a blood pressure registered in 1964 when they were 50 and in 1974 when they were 60. For those 627 participants a straight correlation (with y = x) was found between systolic blood pressure at the age of 50 (SBP_{50}) and SBP_{60}. A well marked scattering was observed (r = 0,54).

In Figs. 1 and 2 participants undergoing hypertensive treatment during the period 1964 to 1974 were excluded. According to systolic blood pressure at the age of 50 the participants were divided in decentiles. In Fig. 1 the same participants were divided in decentiles according to SBP_{60} illustrating the spontaneous change in blood pressure during the decade. The highest decentile of the participants in the baseline examination had SBP ≥ 165 mmHg and might be regarded a "high risk group". Fig. 2 shows that only 13 participants from this group at the age of 60 still belonged to the highest decentile. Twenty probands had drifted towards lower blood pressure values. Simultaneously 58 individuals from the "low risk group" in 1964 progressed to the highest decentile in 1974. We ought to have kept the 9th decentile (baseline blood pressures from 155-160 mmHg) under observation, expecting hypertensives to emerge from this group over time. Thirteen did so. 8 stayed in the 9th decentile, while 24 obtained normal blood pressures. At the same time 39 individuals moved up into the borderline-decentile.

The group belonging to the highest decentile at the age of 50, had a considerable overmortality and overmorbidity 1964-1974. Fifty-six men had SBP_{50} ≥ 160 mmHg. The ten-year mortality in this group was 29% compared to 11% among the 375 men in "the low risk group". The incidence of cardiovascular manifestations (fatal and nonfatal) was 35% in "the high

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Discussion

Agner

The low frequency in 80 year olds may be connected with the fact that patients with hypertension have had some other disease myocardial infarction or something else, which results in a lower blood pressure.

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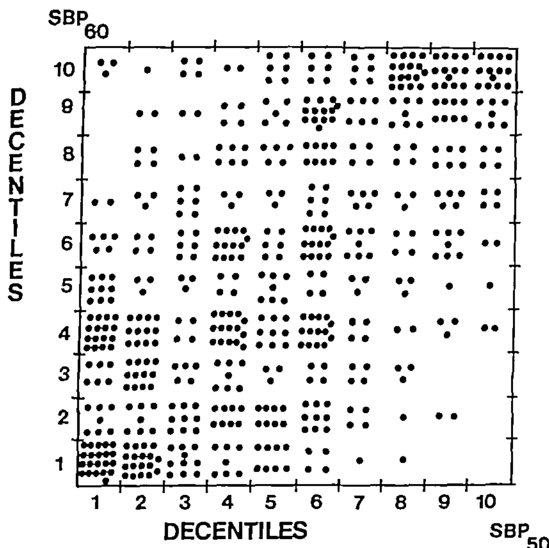


Fig 1 Systolic blood pressure in decentiles aged 50 and 60 from the Glostrup population studies of men and women born in 1914 Participants undergoing hypertensive treatment during the period 1964 74 are excluded

risk group" and 9% in "the low risk group" At the re-examination in 1974 20-30% of the men with high entry blood pressures had angina pectoris intermittent claudica tion and dyspnoea on exercise in contrast to 4-9% of the rest There was an over representation (but not statistically signifi-cant) over hypertensive organ-changes at age 60 among men with high blood pres-sures at entry

The severe consequences of hyperten-sion might be diminished by a transforma tion of the entire blood pressure distribu tion in the population towards lower val ues A large scale weight reduction and im-provement of physical fitness might influ-ence the blood pressure distribution in a population but this is still to be proved

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Discussion.

Poul Ebbe Nielsen.

Is it possible that hypertension sometimes takes a cyclic course with patients passing through high blood pressure periods last

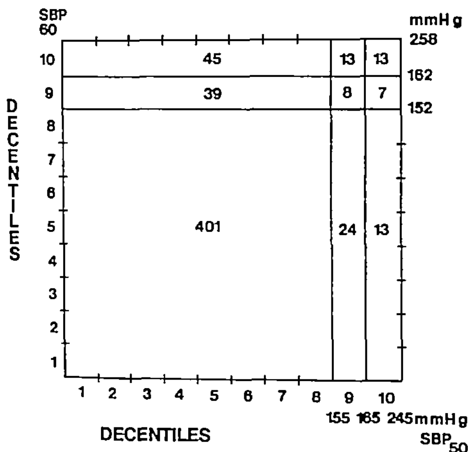


Fig. 2 The spontaneous change from high risk to low risk groups and vice versa over 10-year period illustrated by separating the two highest SBP decentiles in figure 1 at age 50 and 60.

ing months or perhaps years, after which the blood pressure again returns to normal without any form of treatment?

Marianne Schroll.

I have no observations supporting the theory of a cyclic course. However I think it would be interesting in our material to define a group which has not had raised blood pressure to see what characterizes it. So far, we have only concentrated on characterizing the high blood pressure group.

The Prevalence of High Blood Pressure among 40 Year Old Men and Women

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From the Section of Prospective Medicine Medical Department C,
Glostrup County Hospital, Copenhagen, Denmark

The aim of this presentation was to elucidate the following two points

1 The prevalence of hypertension in a population of 40 year old men and women
2 Is screening for high blood pressure possible through the existing Danish health system?

A detailed description of the methods used in the Glostrup population studies has been published elsewhere (1 2, 3) In the present study a population of 1 199 persons born in 1936 and living in Glostrup and three neighbouring municipalities was selected The group was assumed to be representative of the 40 year old men and women in Denmark All were offered a health examination at the Section for Prospective Medicine and the overall response rate was 88% Among the non-participating 12% 61% answered the questionnaire concerning health and occupation either by telephone or in writing When attending the health examination measurement of blood pressure (BP) was carried out by one investigator (H H) The blood pressure measurements were standardized in accordance with the WHO recommendations (4) diastolic BP indicated as phase V (disappearance of the Korotkoff's sounds) using a mercury manometer (5)

BP recordings were carried out in the morning after 5 minutes rest in the sitting position each value representing an average of two determinations The criterion of hypertension was diastolic BP ≥ 95 mmHg in accordance with the WHO recommendation Persons with high BP values were referred to the out-patient hypertension clinic where the diagnosis of hypertension was ascertained by repeated ambulatory BP measurements and aetiological screening was carried out Contacts with the existing Danish health system, i e general practitioners hospitals specialists and emergency wards were assessed by questionnaires

The average casual BP in the population was 124 ± 14 mmHg (mean ± s d) systolic and 82 ± 11 mmHg (mean ± s d.) diastolic. Women had significantly lower BP than men in accordance with earlier investigations. By application of the WHO criteria for hypertension high BP was demonstrated in 9.3% of the population, in a proportion of 3 1 in men and women

Fig 1 shows a flow diagram illustrating the 40 year old population divided according to history of hypertension, actual treatment and BP at the examination Among 143 persons with a history of high BP 21 were on antihypertensive treatment and among the remaining 122 without treatment 32 still had raised BP Among 909 persons without history of hypertension, 57 were found to have an increased BP Thus a total of 110 persons had high BP i e 10% of the population studied In accordance with earlier studies approximately 50% of the cases with high BP were hitherto unknown Forty per cent of the cases with a history of high BP had never received antihypertensive therapy In patients who had been treated for hypertension 30% had discontinued the therapy and only half of the cases on treatment were normotensive at the examination

Until now 53 persons have attended the out-patient hypertension clinic with at least three visits and among these 21 (40%) had

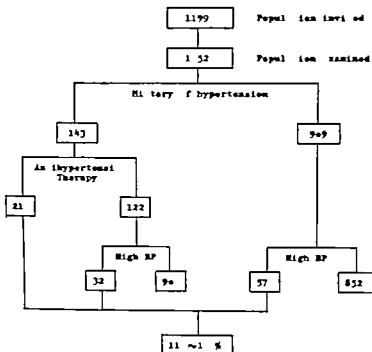


Fig. 1 The 40 year population divided according to history of hypertension, actual treatment and increased blood pressure (diastolic ≥ 95 mHg) at the examination day

a sustained diastolic BP in accordance with the diagnosis hypertension (≥ 95 mmHg diastolic). Renovascular hypertension was not diagnosed in any case. In the population the BP has been previously measured in 88% in 6% it had not and in the remaining 6% no information about BP measurements was available.

In the group without BP recordings 96% were men and 4% women in accordance with the fact that women as a routine have their BP measured during pregnancy

Through an analysis of contacts with the existing Danish health system within the last year the following was found.

Among the non-hospitalized 90% of the population, 531 persons (50%) had consured in 96 (90%)

Among the non-hospitalized 90% of the population, 531 persons (50%) had consulted their general practitioner where the BP was recorded in 265 cases (50%)

Finally among the non-hospitalized population who had not visited the general practitioner 45 persons (4%) had consulted a specialist, where the BP had been measured in 9 cases (20%).

Thus, approximately two-thirds of the 40 year old population have been in contact with the existing health system within the last year but only in half of the cases had a BP measurement actually been performed.

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Cost of Care of the Hypertensive in the Primary Preventive Trial, Gothenburg

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To enable a future discussion of priorities with regard to various medical measures it is necessary to take monetary costs and benefits as well as medical benefits into account

The costs of detecting and treating hypertensives evidently depend upon the structure of the medical care of the community In larger communities with several doctors and hospitals the system will be more complex and expensive than in a smaller area with only one or a few responsible persons Screening of the whole community may be necessary to achieve complete control of all hypertensives

The present report concerns screening and treatment of a random population sample of middle-aged men and is part of a comprehensive primary preventive trial against primarily coronary heart disease (5 7)

Findings during recent years indicate *that* close to 95% of middle-aged hypertensives have primary or essential hypertension (8) Very few hypertensives have a secondary form which can be cured by surgical measures. Thus, the demand for extensive examinations of all hypertensives has been reduced considerably

The costs for drug treatment of hypertensives can vary due to choice of drug; beta-blocking drugs are far more expensive than diuretics If these two drugs were comparable *from a medical point* of view the cheaper drug would be recommended However the recent findings of a possible cardioprotective role of beta-blockers (2, 9) may have great advantage to hypertensives as most of them are threatened by cardiovascular complications (1).

Cost of screening

The intervention group of the Primary Preventive Trial comprised one-third of all men in Gothenburg born in 1915 1922 and 1924-1925 or 10 000 men, and 7 455 of these participated.

The total cost of screening, basic care, check-ups and computer processing of data during the years 1970-1973 was 1 4 million Swedish kroner (S kr) recalculated in terms of the value in 1976 The costs for only hypertension screening and processing of these data have been estimated to be 350 000 S Kr This gives a cost per person of about 50 S.Kr or 550 S.Kr per detected *hypertensive (635 detected at the first examination)*

Cost of diagnosis and follow-up

All the men who had screening blood pressures (BP) ≥ 175 systolic or ≥ 115 diastolic were re-examined within 2 weeks and *refer*

Table I Cost of diagnosis and follow-up of one hypertensive during 5 years. The Primary Preventive Trial, Gothenburg.
Prices in S Kr 1976.

1 Check of diagnosis	
3 BP s by nurse	225
2. *Initial lab tests*	120
3 Start of control of treatment,	
first year 3 visits to a physician	570
3 visits to a nurse	225
4 Yearly lab tests 4 x 50	200
5 Check ups	
4 visits to a physician	750
12 visits to a nurse	900
Total during 5 years	~ 3 000

Table II. Cost of drugs. The Primary Preventive Trial, Gothenburg. N = 633 Prices in S.Kr 1976.

	%	Per pat/yr	Tot/year
Single drugs			
Beta-blockers	18	600	68 400
Diuretics	14	150	13,350
Combinations			
Beta-bl. + Diuret.	26	750	123 750
Beta-bl. + Hydralaz.	24	800	121 600
Beta-bl. + Diuret. + Hydralaz.	14	950	84,550
Other drugs or comb.	4	750	18 750
Total per year			430 400
Mean per patient during 5 years			~ 3 400

red to a special hypertension clinic for further work-up and treatment. Men with lower BP's were also checked and treated if considered necessary. Two hundred and three men were already on treatment at screening, but had BP's below 175 systolic and 115 diastolic.

The costs during 5 years are shown in Table I. It should be stressed that the real costs, and not only the part of it paid by the patients, are included.

Cost of drugs

The various drugs used and the real drug cost appears in Table II.

Cost-benefit analysis

Table III summarizes the costs for detection and treatment during 5 years, about 7,000 S.Kr per hypertensive patient.

According to recently published results an expected mortality of 8% and incidence of 8% of non-fatal myocardial infarctions were both reduced to about half (1). This indicates that 25 men might have been "saved" by this treatment during the five years. This fairly optimistic view on the effect of treatment has not yet been corroborated by other similar results. Thus, we have to be careful about the interpretation of the results. It should be kept in mind that 82% of the patients were treated by beta-blockers which might have had a specific cardioprotective effect in this study. The total cost per "saved life" can be estimated at 168,000 S.Kr

Comparison with other studies

The present costs per "saved person" have been compared in Table IV with those of the

Table III. Cost of detection and treatment during 5 years for one hypertensive. The Primary Preventive Trial, Gothenburg. Prices in S.Kr 1976.

Costs	
Screening	550 (8%)
Diagnosis and follow-up	3,000 (43%)
Drugs	3 400 (49%)
Total per pat.	6,950
Total for 633 pats.	~ 4 400,000

Table IV. Cost per hypertensive prevented from death according to severity of hypertension. S.Kr 1976.

The VA Study	
DBP 115-129	33,500
DBP 90-114	108,000
The Multifactor	
Prev. Trial, Gothenburg	163,000

Calculation based on the mean cost of treatment of hypertensives in Gothenburg.

Veterans Administration Studies in the USA (3 4) It is seen that the cost-benefit ratio is better for groups with more advanced hypertension as in the Veterans Administration Studies It should be pointed out that the screening cut off points 175/115 which were used in the present study are comparable to resting BP s of 162/101 (6) If the prevalence of hypertensive organ *manifestations are compared it is also* found that most hypertensives in the present study had a less severe hypertension than those in the American Studies The prevalence of left ventricular hypertrophy according to ECG was four times higher in the Veterans Administration Study with DBP 90-114 mmHg than in the present study

It is evident that the cost-benefit ratio is dependent upon the severity of hypertension but the costs for saved lives are nevertheless moderate even in moderately severe hypertension

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Expenses Concerning Evaluation and Treatment of Hypertension

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Copenhagen, Denmark

In view of the high frequency of hypertension in the community the costs concerning evaluation and treatment of these patients are of great socio-economic interest. The extent of the examinations, the purpose of which is to identify hypertensive organ damages and to discover any secondary curable forms, is controversial. One of the reasons is the costs involved.

An examination programme regarding patients with high blood pressure referred to an out-patient clinic has been set up (Table I). The physical examination and the circumstances about the blood pressure measurement will not be mentioned in this study. Routine laboratory tests including ECG and X-ray of the chest are recommended for all patients. For patients re-

Table I. Recommended examinations in different patient groups.

Examinations	Groups I–IV	No of pats.		%
Hemoglobin, serum creatinine, serum potassium, urine analysis protein/glucose and microscopy, ECG, X-ray of the chest	*Group I*			
	1. pats. without indication for treatment	52	80	34
	2. pats. ≥ 70 years in spite of indication for treatment	28		
As above + isotope renography	*Group II* pats. with indication for treatment			
	1. diastolic BP ≥ 105 mmHg	76	106	46
	2. hypertensive organ damages	30		
As above + rapid sequence pyelography	*Group III*			
	1. pats. < 50 years, diastolic BP > 115	27	43	19
	2. all ages, diastolic BP > 130	7		
	3. sudden aggravation of the hypertension	2		
	4. drug treatment proves unsatisfactory	7		
As above + renal aortography + renin concentration in renal veins	*Group IV* suggestion of renal/renovascular cause of the hypertension		3	1

Veterans Administration Studies in the USA (3 4) It is seen that the cost benefit ratio is better for groups with more ad vanced hypertension as in the Veterans Ad ministration Studies. It should be pointed out that the screening cut off points 175/ 115 which were used in the present study are comparable to resting BP s of 162/101 (6) If the prevalence of hypertensive organ manifestations are compared it is also found that most hypertensives in the pre sent study had a less severe hypertension than those in the American Studies The prevalence of left ventricular hypertrophy according to ECG was four times higher in the Veterans Administration Study with DBP 90-114 mmHg than in the present study

It is evident that the cost-benefit ratio is dependent upon the severity of hypertension, but the costs for saved lives are never theless moderate even in moderately severe hypertension.

References

1 Berglund, G Wilhelmsen, L. Sannerstedt, R. Hansson L Andersson, O., Sivertsson, R Wedel, H & Wikstrand, J Decrease of CHD morbidity by treatment of hypertension. Lancet 1978,I 1

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An examination programme regarding patients with high blood pressure referred to an out-patient clinic has been set up (Table I) The physical examination and the circumstances about the blood pressure measurement will not be mentioned in this study Routine laboratory tests including ECG and X-ray of the chest are recommended for all patients. For patients re

Table I. Recommended examinations in different patient groups.

Examinations	Groups I IV	No of pats.		%
Hemoglobin, serum creatinine serum potassium urine analysis protein/glucose and microscopy ECG X-ray of the chest	*Group I*			
	1 pats. without indication for treatment	52	80	34
	2. pats. ≥ 70 years, in spite of indication for treatment	28		
As above + isotope renography	*Group II* pats. with indication for treatment			
	1 diastolic BP ≥ 105 mmHg	76	106	46
	2. hypertensive organ damages	30		
As above + rapid sequence pyelography	*Group III*			
	1 pats. < 50 years, diastolic BP > 115	27	43	19
	2. all ages, diastolic BP > 130	7		
	3 sudden aggravation of the hypertension	2		
	4 drug treatment proves unsatisfactory	7		
As above + renal aortography + renin concentration in renal veins	*Group IV* suggestion of renal/renovascular cause of the hypertension		3	1

Table II. Distribution of indications for treatment

	Group I	Group II	Group III	Group IV	Total	%
Level of blood pressure only	16	76	29	2	123	68
Cardiac abnormalities	11	21	8	1	41	23
CNS abnormalities	1	5	3		9	5
Cardiac + CNS abnormalities		3	2		5	3
Optic fundi changes (grade III)			1		1	
Pats < 40 years (grade II)		1			1	
Organ damages only	2	4			6	3

quiring treatment isotope renography is suggested. This examination may not be strictly necessary Rapid sequence pyelography is recommended for the selected patients shown in group III The choice of isotope renography previous to rapid sequence pyelography is based on the fact that this examination is quicker and more comfortable for the patient and in addition it is less expensive Finally more complex diagnostic procedures to discover renal/renovascular diseases can be reserved for patients in whom the above mentioned examinations suggest one of these as a cause of hypertension

In order to demonstrate the distribution of patients into the four groups patients of two particular years 1974 and 1976 were examined retrospectively The patients were referred to our out-patient clinic by general practitioners because of hypertension, often for reasons of convenience or difficulties in the treatment. The material comprised 232 patients 110 men and 122 women The average age was 54 years, 34% under 50 years, 28% from 50 to 59 years and 38% over 60 years old. Table I shows the distribution of the material into the four groups Less than 2% belonged to group IV

The indication for treatment is seen in Table II The level of blood pressure was the only indication in 70% of the cases Visceral changes were found in 30% and visceral changes as the only indication in 3% In 70% of the cases ophthalmoscopic examination was performed by a specialist. Owing to the rare occurrence of premalignant retinal changes ophthalmoscopic examination is not included in the evaluation programmes It should be mentioned, however that the examination perhaps ought to be done in young persons having borderline blood pressure.

Table III presents the final therapeutic regimen A change in the use of drugs has been made namely from methyldopa to beta-blockers.

The average expense of medicine per patient was D Kr 4.20 a day a little more in 1976 than in 1974 The cost of examinations in group I is D.Kr 350 00 in group II D Kr 500 00, in group III D Kr 700 00 and in group IV D Kr 10 000 00 The calculations are based on the fact that the examinations in groups I II and III are performed at an out-patient clinic, whereas the examinations in group IV are based on admission to hospital estimated at 10 days at a price of D Kr 1000 00 each.

The purpose of the present paper is to demonstrate that the vast majority of hypertensive patients can be evaluated at moderate costs In 80% of the patients referred examinations in group I or II will be adequate, in 18% or 19% goup III examinations will be adequate and only in less than 2% will admission to hospital be nec

Table III. Use of drugs in different diagnostic groups in 1974 and 1976.

	1974 (total 80 pats.)		1976 (total 96 pats.)	
	Groups I + II	Group III	Groups I + II	Group III
Diuretic only	29%	4%	30%	3%
Diuretic + methyldopa	16%	3%	8%	1%
Beta-blocker only	9%	6%	11%	2%
Beta-blocker + diuretic	15%	4%	16%	11%
Beta-blocker + diuretic + vasodilator	1%	8%	3%	7%
Other combinations	5%	1%	8%	

essary. Our evaluation programme is of course characterized by the fact that it is carried out at an out-patient clinic. The general practitioner might be still more economical, especially regarding patients not requiring treatment.

It is, however questionable whether the present material represents the population seen by the general practitioner. To some extent reference to an out-patient clinic may have sorted out very mild cases, and therefore our calculations do not make too favourable an impression of the economic strains.

We think that our experiences may be helpful when the expenses regarding an investigation of the population are to be evaluated in respect to screening, evaluation and treatment of high blood pressure.

Discussion:

Giese:

This, then, is an investigatory programme geared to patients who are referred to a special hypertension clinic. There is no question of it being a limited investigation. Presumably this is an important primary condition.

I would think that the extra examinations in groups III and IV are completely unnecessary if renography in group II is carried out lege artis and shows completely negative results. If the serum creatinine and urine examinations are also normal it would be very very rare to find anything by more extensive examinations. If one wants to go further I do not believe that it should be done with wash-out urography. Then it would be more important to examine the renal vessels direct by angiography.

I do not understand why ophthalmoscopy is not included in the programme. The retina is the only place in the organism where the vessels can be seen direct. Surely it must be very important for a complete evaluation of the patient to know whether there are changes in the retina, especially with regard to the risk of stroke.

Hilden:

Giese is probably right in what he says: If the isotope renography is normal, we can at least leave out urography in our group III. After all, it can be combined in various ways. But what we saw as our first concern was to show how large a proportion of patients there are who actually only need a very modest programme of examinations.

Eye examinations are traditionally included in all examinations for hypertension, and at one time have had an enormous importance Neither would I say that ophthalmoscopy should not be used at least in younger patients, but one should not expect too much from it If an indication for treatment is based on repeated confirmations of raised diastolic blood pressure, virtually all patients with eye changes will receive treatment and it will not be the eye changes as such that will supply the indication for treatment

Standardized Investigation Programme on Patients with Hypertension a Cost Analysis

SVEN ÅKE FORSBERG
From the Department of Medicine,
Borås Hospital, Sweden

Working since 1969 with a standardized programme for hypertension at the medical clinic of Borås Hospital, we have made an attempt to evaluate the costs of what is called a basic or minimized investigation of uncomplicated cases of hypertension

We imagined an average patient a textile worker as Borås is the textile centre of Sweden. He lives four kilometers from the hospital, works, and when absent his salary is correspondingly reduced. The patient has been referred to the hospital by a doctor during 1973 The hypertension dispensary is part of the activities at the policlinic of the medical clinic.

On these conditions, we made a flow analysis of all details included in a basic investigation for hypertensives. Table I gives the different steps. The process of patient reference consists of the work of doctors, secretaries and the post office department. The first three visits to the hospital include the diagnostic part. At the third visit the doctor medically examines the patient, completes the special medical record for hypertensives and starts the treatment. The result of treatment is checked by the dispensary assistant at the fourth visit. At the fifth visit to the doctor the pressure is assumed to be normalized and thereafter follows the regular half year check-ups.

Table II gives an example of how the cost factors at the third visit were analyzed The time spent at the different working times was estimated from interviews and direct measurements. The working times and the corresponding costs were distributed among the different categories of employees. The salary costs include the employer's social salary expenses to the State.

At Borås Hospital a statement of account is applied which is based on different local organizations, of which the medical policlinic is one. The policlinic costs excluding salaries were calculated from the total expenses at the medical policlinic minus salaries. The patients at the hypertension dispensary were assumed to take a part of these costs proportional to their number in relation to all patients at the medical policlinic during 1973

The expenses originating from laboratory analyses were calculated from the scores generally used by Swedish hospital laboratories for their cost analyses

The patient's loss of net salary was estimated at 45 per cent of the gross income assuming a taxation of 55 per cent. These 55 per cent constitute the State's loss, when the patient does not work, plus 30 per cent of the gross income which is the social salary expense the employer has to pay to the State. Drug expenses were excluded from the study

Table III comprises the final cost analy-

Table I Basic or minimized investigation in hypertension

1 The process of patient reference
2. The first visit test sampling by the dispensary assistant
3 The second visit pressure measurement by the dispensary assistant
4 The third visit medical examination by the doctor Start of treatment.
5 Organization of treatment check-ups
6. The fourth visit pressure control by dispensary assistant
7 The fifth visit the doctor checks the treatment

Table II The first visit to the dispensary assistant

1 The journey of the patient to and from the hospital	
2. Time of absence from work	
3 Test sampling	
a Height	d Blood sample
b Weight	e. ECG record
c. Urine sample	f Blood pressure measurement
4 Laboratory analyses	
a Urine protein test	f Serum potassium
b Urine glucose test	g Serum urate
c Urine bacterial test	h Serum calcium
d. Blood hemoglobin	i. Serum cholesterol
e. Serum-creatinine	j Serum triglycerides
5 The administration of the patient	
6 Administration of the medical record	

sis Of cost factors "Policlinic" means the total costs at the medical policlinic minus salaries to the employees there. The ex penses are distributed over the three main carriers of costs In Sweden "Landstinget" an organization somewhat similar to the county council is responsible for all public medical care.

One should be fully aware of the theoretical character of the presumptions which can be criticised For example the em ployer s loss when the worker is excluded from production has not been estimated because we found it impossible. The policlinic fee the patient has to pay is an income for "Landstinget" and therefore reduces their costs from 265 to 241 kronor Owing to inflation the sums given in table III should be increased approximately 30 per cent to get figures valid for 1977

A detailed flow analysis of investigational procedures gives ideas about cost saving changes The study also discloses the big saving it should mean to organize hyper tension dispensary in the evenings for working people and to let nurses employed at industries measure blood pressure under standardized conditions during working hours.

Reference

1 Forsberg, S.Å. and Oscarsson, C. The content of the basic investigation a flow analysis and calculation of costs (in Swedish) From Omhändertagande a hypertoni/74 Lindgren & Söner AB, Mölndal, 1975

Table III The final result of the cost analysis given in Swedish kronor

Cost factors	Cost carrier Landstinget	Cost carrier The patient	Loss of taxation The state
Salaries of employees	142		
Policlinic + postage	48		
Laboratory analyses	75		
Policlinic fee	24	24	
Travel costs		15	
Loss of salary		141	268
Totals	241	180	268

The sum of subtotals = 689 Swedish kronor

Discussion:

Wasler

It is important to separate real economy and financial policy Forsberg s table contained three columns each of which was interesting, namely the costs of diagnosis and treatment, economic loss to the patient, and the tax loss to society respectively However they cannot just be added together There are two groups of costs that are financially important to society namely the costs spent on diagnosis and treatment, and the loss of production owing to the patient s examination and treatment. On the other hand, the way in which the patient earns his money does not play an economic role in society even though it is important to the patient himself Taxes have no real economic importance, they are only transfers of money from one group of society to another

Table II The first visit to the dispensary assistant.

1 The journey of the patient to and from the hospital

2. Time of absence from work

3 Test sampling

a. Height	d Blood sample
b Weight	e. ECG record
c Urine sample	f Blood pressure measurement

4 Laboratory analyses

a Urine protein test	f Serum potassium
b Urine glucose test	g Serum urate
c. Urine bacterial test	h Serum calcium
d Blood hemoglobin	i Serum cholesterol
e Serum-creatinine	j *Serum triglycerides*

5 The administration of the patient

6 Administration of the medical record

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One should be fully aware of the theoretical character of the presumptions, which can be criticised For example the employer's loss when the worker is excluded from production has not been estimated because we found it impossible The policlinic fee the patient has to pay is an income for "Landstinget" and therefore reduces their costs from 265 to 241 kronor Owing to inflation the sums given in table III should be increased approximately 30 per cent to get figures valid for 1977

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Totals	241	180	268

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should be allowed to participate in taking the decision of setting up and carrying out the project in the different departments.

The registration can be made using dif ferent patients from the accident and emer gency department, the out-patient depart ment, the operating theatre department, and the standard acute ward, and the re- sults still can be coordinated so as to give a comprehensive picture of the process involved with treating a typical patient s illness within the hospital.

The results of the preliminary study on the examination, treatment and nursing process within the hospital has now been published, in a report which can be obtained from the
Danish Hospital Institute
Landemaerket 10
DK 1119 Copenhagen K
Denmark.

Discussion:

Olesen:
The kind of analysis that the Danish Hospital Institute is carrying out where a real effort is made to find out what is being done, is far too rare in the medical world. I think it would be very interesting to know how many superfluous clinical examinations are being made. There are medical departments that completely perform three objective investigations with varying de grees of superficiality and this is rather expensive. Much would be gained by de termining how the hypertensive patient should be clinically examined, and at which level of training and experience. There is much talk about how large a role hyper tension plays in health costs. I think it is also very important to look at the question from the point of view: How large a per centage of hospitalized patients have problems that in actual fact are caused or complicated by or associated with hypertension? I am thinking in particular of apoplexy and cardiac infarction.

Hilden.
There is probably no answer to that question. To the Danish Hospital Institute I would say that in my opinion very few patients with hypertension should be hospitalized, and those are the ones who should be ex amined by the more complicated methods which require the patient to be kept under close observation. I suppose that that would be 2% 3%

Henning Poulsen.
The Danish Hospital Institute does not decide who should be hospitalized or who should be treated as out-patients. We only analyse the situation as it is. We believe that hypertension is a suitable disease for inclusion in our investigation programme on examination, treatment and care because here we have the opportunity of evaluating alternative therapy In the next few years, we shall extend these investigations to cover very large surgical and medical diagnostic groups, so we should get a complete picture of what actually happens with patients in the Danish hospital and health services.

Hilden.
I know very well that in Denmark many patients with hypertension are admitted to the medical wards In reality there are only three kinds of medical patients, the acute, the out-patient and the nursing home patient.

Hervald.
No one today can say whether it is better to hospitalize patients or to put them through a programme of out-patient ex aminations. I think it may be important to get an impression of the 24 hour blood pressure, to see how the initial treatment affects the patient, and to teach the patient to follow the treatment.

Arterial Hypertension, Examination, Treatment and Nursing Processes in Primary Health Sector and Hospital

NIELS HOLM-NIELSEN MOGENS KJÆRGÅRD HANSEN and HENNING POULSEN
From the Danish Hospital Institute,
Copenhagen, Denmark

The Danish Hospital Institute is an independent institution which was set up in 1975 with the main purpose of collecting and disseminating information in the hospital and health service field at the same time carrying out developmental research into planning rationalisation and management The aim is to provide a better basis for solving the problems faced by the planning and governing authorities within the health services

The institute has carried out two preliminary studies on the examination treatment and nursing processes one within the primary health sector (private practice) and the other correspondingly within the hospital.

The main aim is to develop a system for defining the processes undertaken and to show the extent of the cooperation involved between the two main sectors of health care and the ways in which there is cooperation with the social sector so that the total process of the illness can be established There is a need for setting out the actual activities which are undertaken during a patient s illness and to that end the processes which result from a diagnosis of arterial hypertension and intertrochanteric fracture of the femur are being registered and analysed

The pilot study which deals with the activities undertaken by the private practitioner was started in the summer of 1976 and 86 practitioners are taking part representing 53 practices situated in 4 different counties. The choice of the participants covers a variety of conditions, e.g. with regard to distance to the nearest hospital dispensary and social services, the number of doctors in the practice, the number of nursing staff available, the number of patients registered with the practice, the way the practice is run and the system used for working shifts etc. The preliminary study will be completed by February 1978 The method which has been developed should with regard to both projects be able to be used locally so that the staff involved will themselves be able to register the information required This will later form the basis for a general discussion and evaluation to be undertaken at a conference Here it should be possible for experts to assess the priorities and planning of the services required for the examination treatment and nursing of the chosen illnesses in Denmark

The different systems which are in use locally for the examination, treatment and nursing process should be registered and the requirements set out for resources where not only the effect of the treatment is evaluated

In the same way as with the private practice a similar study has been undertaken during the period of one year to set up a system of evaluation for the hospital sector The registration has taken place at three university hospital departments both surgical and medical standard acute wards and out-patient departments involving over 125 hospital staff of various categories

The primary study undertaken within the hospital has shown that it is in fact possible to register activities in this way The differing characteristics of the various departments have shown that it is most important that all the staff groups involved

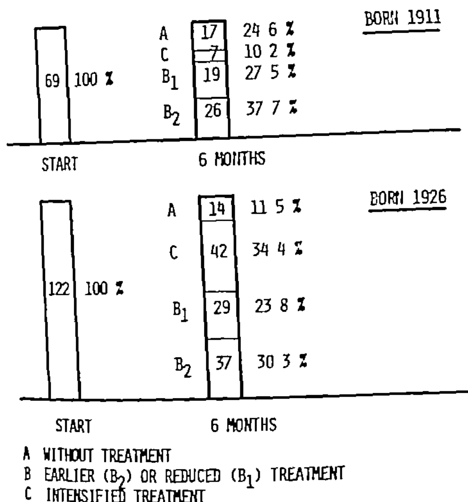


Fig. 1. Antihypertensive treatment of patients born in 1911 and 1926.

drawal of drugs does not cause a rise in the blood pressure, some remaining at the normotensive level.

Studies in search of the causes which lead to inappropriate treatment in hypertension are still in progress.

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How to Avoid Inappropriate Antihypertensive Treatment

A. EISALO and K.J TÖTTERMAN
From the First Department of Medicine, University Central Hospital, Helsinki Finland

Traditionally early diagnosis of hypertension is stressed followed by adequate treatment and careful follow-up of the patient The reference point related to these aspects is the normotensive value. On the other hand inappropriate treatment, involving the use of an excessive amount of drugs may result if the hypertensive condition is evaluated only by the normotensive value A reduction in the administration of useless drugs may lead to a diminution of side effects as well as placing the subject treatment on a sounder economic basis. The purpose of our study is to examine if antihypertensive treatment can be excessive In this paper we shall show the preliminary results of our progressive study

Helsinki resident hypertensive patients born in the years 1911 and 1926 who have used antihypertensive agents for at least 5 years were selected as the subjects of our study Their names were obtained from the social insurance files in which all hypertensive patients are listed as they receive the necessary drugs free of charge. Primarily patients who had suffered a stroke congestive heart failure and renal failure were excluded A total of 415 were called and 209 were admitted to the study In the first visit 9 patients were excluded because of hemiplegia, congestive heart failure, intermittent claudication and psychosis During the first month of the follow-up period 9 dropped out because of an uncooperative attitude, acute psychosis stroke, and hemiplegia. Thus a total of 191 patients were admitted to follow-up (Fig. 1) Sixty-nine were born in 1911 (30 men and 39 women) 122 were born in 1926 (52 men and 70 women) A complete physical examination including chest X-ray ECG and serum potassium was taken during the first visit. To date the time span of the follow-up period has reached 9 months.

Blood pressure in women born in 1911 (39 patients) In 21 patients the treatment was withdrawn but 13 had to be retreated. In 14 patients a reduction in the daily dosage did not cause a rise in blood pressure, some remaining normotensive In 3 patients the initial blood pressure reading was high and the treatment had to be intensified

Blood pressure in men born in 1911 (30 patients) In 17 patients the treatment was withdrawn initially Nine cases had to be retreated It was possible to reduce the dosage in 5 patients but it had to be intensified in 4 patients.

Blood pressure in women born in 1926 (70 patients) In 12 patients the treatment was withdrawn initially Eight cases had to be retreated. The dosage was reduced in 25 patients initially and the reduction was slowly continued so that it was possible to withdraw the treatment in 7 additional patients Thus 11 out of the 70 patients were normotensive and did not require any antihypertensive regimen In 23 patients the treatment had to be intensified.

Blood pressure in men born in 1926 (52 patients) Initially in 10 patients the drugs were withdrawn. Seven cases had to be retreated. In 11 patients it was possible to reduce the daily dosage and in 19 it had to be intensified

The preliminary results show that inadequate therapy in hypertension is a problem in all respects Not only may the normotensive level be unattainable but there is a surprisingly large group in which a reduction of the daily dosage or even with

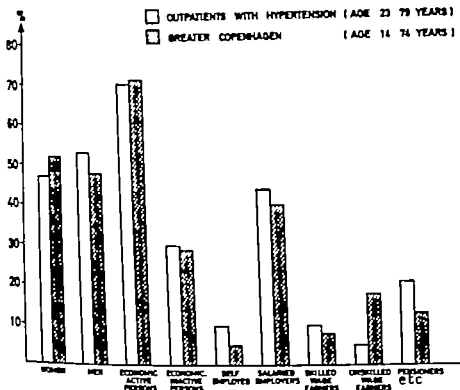


Fig. 1 Employment situation of 277 out-patients with moderate and severe hypertension compared to that of the population in Greater Copenhagen.

economically active women and significantly ($P < 0.01$) more women who receive disability pensions in the group which have been treated for more than 6 years. This difference cannot be due to the small, but insignificant, difference in age groups, neither can it be due to differences in the severity of hypertension (as judged by the WHO-staging). Though there are more patients with WHO II and III in the group treated for more than 6 years, this difference is far more pronounced among the men.

Two hundred and twenty-eight patients (83% of the material) have or have had an income. Out of these 228 patients, 13%

Table II. Relation between duration of treatment, sex and economic situation among 180 hypertensive patients aged 40 to 60.

	Duration of treatment			
	< 6 years		> 6 years	
	Women	Men	Women	Men
Number of patients	48	56	36	40
Mean age (years)	48 7	51 9	51.6	51 7
WHO II + III	29 (60%)	29 (52%)	24 (67%)	36 (90%)
Economically active[1]	46 (96%)	54 (96%)	25 (69%)	38 (96%)
Disablement pension	2 (4%)	2 (4%)	11 (31%)	2 (4%)

[1] Including housewives and unemployed.

The Social and Psychological Consequences of being Long term Treated for Moderate and Severe Hypertension

MARTIN DØSSING LIS KELSTRUP and TAGE HILDEN
From the Department of Medicine C, Diakonissestiftelsen,
Copenhagen Denmark

The prognostic advantage of medical treatment of hypertension is well established The social and psychological consequences of having a blood pressure which requires life-long treatment and frequent controls are less well illuminated. The purpose of this investigation is to draw attention to these aspects of hypertension

The material includes patients treated at the hypertension out-patient clinic of Diakonissestiftelsen either because of difficulties of control or for research reasons. The patients have been under observation for so long that the medical treatment has achieved a constant level We have left out 3 patients in whom other diseases were of more importance with regard to their social situation.

A questionnaire was sent to 305 patients and 277 answered the questions (91%)

Issues included in the questions

1 The duration of the antihypertensive treatment. With few exceptions this corresponds to the time the patients have been treated in our out-patient clinic
2 Employment situation and economic situation.
3 The influence of hypertension on the employment situation and income
4 The payment of the antihypertensive drugs and the possible strain on the personal economic situation
5 The influence of hypertension on the social and private lives of the patients.

Among the respondents 53% were men and 47% women. Two-thirds of the patients were between 40 and 60 years old, the average age being 53 years.

The results of the WHO-staging and the duration of treatment are shown in Table I

Table I Severity of hypertension according to WHO criteria. Duration of antihypertensive therapy

Severity of hypertension		Duration of treatment	
WHO I	33%	2 years	13%
WHO II	62%	2-6 years	42%
WHO III	5%	6 years	44%

Most of the patients have visceral changes corresponding to WHO II and have been treated for more than two years

The employment situation of the patients compared to that of Greater Copenhagen, is shown in Fig 1 With certain reservations (the proportion of age groups is different and the employment classification of the population of Greater Copenhagen dates from 2 years before ours) the patients will be seen to be about as economically active as the rest of the population The column "pensioners etc." which includes the disabled pensioners early old-age pensioners, old-age pensioners, housewives unemployed and students constitute a relatively higher percentage of the patients. This may be due to the fact that 13% of the patients receive disability pensions and early-old-age pensions because of their hypertension

In Table II the 40 to 60-year-olds are grouped according to sex and duration of treatment. In each of the four groups it has been shown how many of the patients are economically active (including housewives and unemployed) and how many receive disability pensions owing to hypertension. The economic situation of the men is independent of the duration of treatment, but there are significantly ($P < 0.01$) fewer

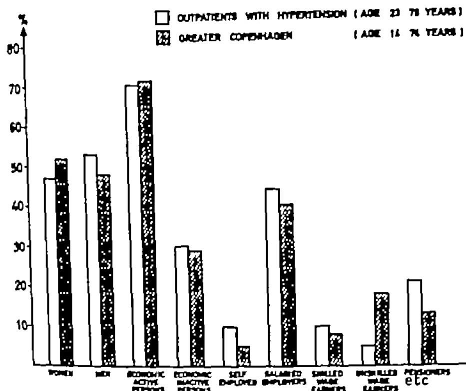


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Mean age (years)	48.7	51.9	51.6	51.7
WHO II + III	29 (60%)	29 (52%)	24 (67%)	36 (90%)
Economically active[1]	46 (96%)	54 (96%)	25 (69%)	38 (96%)
Disablement pension	2 (4%)	2 (4%)	11 (31%)	2 (4%)

[1] [illegible] housewives and unemployed.

Table III Influence of hypertension on the patients activities

The influence of hypertension on the patients life in general (n = 265)	
No influence	39%
Little influence	36%
Strong influence	15%
Do not know	10%
The influence of hypertension on the patients private life (n = 257)	
No influence	54%
Little influence	25%
Strong influence	8%
Do not know	13%

have suffered a decrease in wages without changing their jobs and 6% have had to change their jobs with a decrease of wages as a consequence.

In Denmark the National Health Insurance pay three-quarters of the expenses of antihypertensive drugs for all patients. Patients with low income also have the last one-quarter paid by social support but two-thirds of our patients pay the last one-quarter themselves Of these patients 28% feel this as a certain strain on the economy

Table III shows the distribution of answers to questions as to whether hypertension affects the social and private lives of the patients About 50% feel that the hypertension is a strain on their daily life as it means decreased working capacity no travelling no more sport etc

Approximately one-third of the patients think that their hypertension has a negative influence on their private lives in the form of less time with the family poorer marital relations and less surplus energy to take care of the children. Among the male patients stating that the influence on their private life is strong many gave impotency as the cause. Most of these patients were given beta-blocking treatment and by looking through the journals in retrospect, it turned out that few of these patients had mentioned their impotency to the doctor at the out-patient clinic.

The results of the investigation only refer to patients with moderate and severe hypertension who can be treated as out patients Mild cases of hypertension are referred to their general practitioners and very severe cases with disabling complications cannot be treated as out-patients

The investigation shows that the patients are almost as economically active as the rest of the population of Greater Copenhagen. Those among the patients who can not keep their jobs are women who before giving up their jobs had a low occupational position and had their house work to do and had been treated for more than 6 years.

One has to be cautious when concluding from a vertical investigation based on questionnaires. On the other hand, a considerable part of the patients feel that a number of limitations in their way of life are consequences of their disease and the medical treatment and this must be taken seriously

Programmed Medical Care in Hypertension
Concepts and Ideas

SVEN ÅKE FORSBERG
From the Department of Medicine,
Boden Hospital, Sweden

According to published results conventional medical care of hypertension tends to be of bad quality (4 5). By conventional I mean medical care asked for by the patients at policlinics or practitioners, where many different diseases are treated by doctors in a way depending on the experience and knowledge of the individual doctor

The consequence must be for society to aim at the creation of an alternative and better medical care for hypertensives. This alternative is programmed medical care. This implies that skilled people develop a plan and strategy for detection, investigation, treatment and control of a disease worth treating. The details of a programme must be locally modified due to varying local conditions.

In Sweden the first attempt to develop a programme for hypertension started in 1969 (2). In 1975 the National Board of Health and Welfare in Sweden appointed a committee with the purpose of developing programmes for diabetes, hypertension, urinary tract infection, lump in the breast, hernia and acute tablet intoxication. The programme for hypertension is in progress.

A group of strictly scientifically oriented people is doomed to fail in developing a programme applying to primary medical care far away from universities. A project committee must contain representatives from different levels of medical care and different levels of medical employees.

Until nationwide blood pressure screening programme is organised in Sweden, if ever we shall learn to detect hypertension more often than hitherto by letting blood pressure recording become much more of a routine method in medical care. This can be best accomplished by leaving blood pressure measurement in the hands of nurses and medical aids, by definition of minimal action-demanding pressure level and by creating local channels whereby patients with hypertension can be easily transferred for further investigation.

A basic investigation in hypertension is focused around "The five questions"

1 Hypertension?
2. Affection of the heart, the kidneys, or the brain?
3 What stage of hypertension?
4 Curable hypertension?
5 Does the clinical picture influence choice of therapy?

The first question deals with quality of blood pressure measurements, repeated measurements and definition of minimal action-demanding pressure level.

The second question is about indication for therapy and long term prognosis.

With answers to the first two questions there is also an answer to the third in terms of WHO' classification system for example.

Excluding hypertension caused by oral contraceptives, curable hypertension seems to constitute not more than a few per thousand of all unselected hypertensives (1) Certain simple tests, such as palpation of the femoral pulsations, tests for urinary protein and bacteriuria, analyses of serum creatinine and potassium, can call attention to patients with secondary hypertension of which only a few may be curable In other

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cases only special and individual clinical traits should motivate extended investigations

Question five mainly deals with diabetes gout and obstructive lung disease.

By basic or minimized investigation we mean the degree of evaluation that every patient should be guaranteed (3) It should be adequate for the great majority of patients The basic investigation at Borås Hospital lacks roentgen picture of the lungs and heart i v pyelography and renography We do not check urinary concentration capacity and do not make a urine culture This policy was first met with opposition but recent epidemiological studies have given support to the idea of a simple but consistent investigational programme in uncomplicated cases It is even economically necessary if we are to be able to treat all hypertensives who can be helped.

A programme for hypertension can be applied within the frames of conventional medical care for example by a general practitioner One can also concentrate hypertensives at particular times of the week and thereby perhaps rationalize the work. An alternative is to organize special dispensaries for hypertensives with personnel trained to do their job All three forms of organization are probably appropriate under particular conditions

Two concepts should be used one the minimal action-demanding blood pressure the other the minimal treatment-demanding blood pressure By minimal action-demanding pressure I mean the lowest pressure level recorded on a single occasion motivating further action such as repeated measurements under standardized conditions possibly together with a basic investigation. Minimal treatment-demanding pressure should be defined on the basis of the mean of at least three pressure measurements under standardized conditions. At a certain level the pressure alone indicates therapy and at a specified lower level treatment may be considered together with contributing indications such as heredity sex, secondary organ injury or other cardiovascular risk factors

A hypertension programme should include at least three drugs for use in the majority of patients It is reasonable to have a thiazide drug and a beta-blocker What the third drug should be one cannot be *dogmatic* about At Borås we use hydralazine The choice of alternative drugs in case of side effects or therapeutic failure is yet more uncertain I myself mostly give furosemide, spironolactone or methyldopa

It is important to distinguish the phase of blood pressure lowering from the phase of control of a pressure which has been normalized. One is a dynamic, the other a static phase After a long time of normal pressure one can often, but not always, decrease the amount of medication This ought to be systematically tested according to the principle of minimized medication to achieve normotension

The control of hypertension must be offensive implying that all patients should get written information about time of control and patients who fail to appear for control should be actively traced. Several studies show that such a policy secures good adherence to therapy Information to the patient about hypertension also helps the patient to stick to therapy Therefore all patients should get a booklet about hypertension. In Sweden there are presently about six different booklets to choose between

Home pressure recording is another element of information to the patient about his disease In some cases it is a good help during phases of changing therapy However more research about home pressure recording is needed to exploit the full potential of its use

Some final words of warning We, who start the big and heavy wheels of a machine must also look at means to brake these wheels so that they do not run away We must remember that even if we practically must work with the concept of minimal treatment-demanding pressure we do not really know what that is either medically or economically Presently we simply make the best possible guess

MANAGEMENT PROGRAM FOR HYPERTENSION

THE COUNTY OF SKARABORG
260 000 inhabitants
16 municipalities

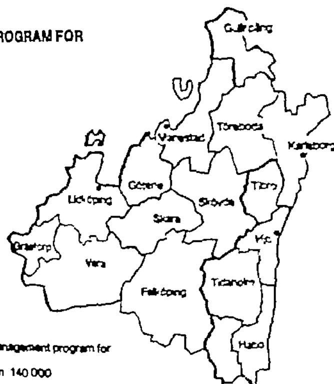


Fig 1. A map of the county of Skaraborg indicating the trial and control areas

control area. The programme is started step-wise. In the first step the management of already known hypertensive patients will be improved through the introduction of special guidelines for diagnosis, treatment and follow-up. These guidelines will be detailed below. In the second step hitherto unknown hypertensives will be traced through the introduction of an obligatory blood pressure measurement for all patients seeking attendance at the primary services, i.e. general physicians and health physicians. This applies only to patients 40-69 years of age. Under that age hypertension is infrequent and firm criteria for treatment cannot be set, and in older patients treatment is less obligatory. Special routines have been worked out for the handling of subjects with hypertension. Newly detected cases as well as previously known hypertensives will be taken care of at The Health Care Centres at which an afternoon per week has been devoted to care of hypertensive patients. An out-patient hypertension clinic has been started at the Central Hospital in Skövde which is the largest town in Skaraborg County and the centre for the Skaraborg project. This central hypertension clinic should serve as a referral station for hypertensive patients refractory to ordinary treatment and for patients with suspected secondary hypertension.

During the third step a complete control of the hypertensive disease is sought to be attained in the whole study area. Subjects with borderline blood pressure will be followed by repeated blood pressure measurements. Diagnostic work-up and treatment will be given in accordance with the guidelines below.

Guidelines for diagnosis, treatment and follow-up

The subjects (40-69 years of age) who are found to have blood pressure above 170 systolic and/or 105 diastolic at the first measurement are offered a check-up within

The Skaraborg Project - A Controlled Trial Regarding the Effect of Structured Hypertension Care

GÖRAN BERGLUND SVEN-OLOF ISACSSON and LARS RYDÉN
From the Department of Medicine I University of Gothenburg
Department of Preventive Medicine and Department of Medicine
the Central Hospital Skövde, Sweden

During autumn 1976 and spring 1977 a care programme for hypertension was worked out This programme is now carried out with start July 1 1977 The work with the programme was initiated by SPRI the Swedish Planning and Rationalization Institute of the Health and Social Services who also financed its development

The background to the growing interest in methods for a better management of hypertension is the fact that high blood pressure is a disease which occurs with a high frequency and is associated with a high risk for future cardiovascular diseases Diseases related to hypertension impose the greatest burden on somatic hospital care in Scandinavia. Half of the hypertensives are unknown to the medical care system and only every seventh hypertensive patient has an acceptable blood pressure control. The health care system in its present form has not been able to overcome this disease

Table I Structure and responsibilities of the central hypertension unit

1 *Structure*

A) Chief cardiologist at the central hospital and chief physician at the department of preventive medicine
B) One district physician
C) One physician from the department of medicine
D) Two nurses.

2. *Definition of duties*

A) To design the hypertension care programme
B) Continual follow up of medical progress and revision of the care programme.
C) Training of personnel.
D) Coordination of hypertension care in the County
E) Collection of data.
F) Processing of data
G) To guarantee management of referred hypertensive patients with complications

The working out of the care programme

This started with a meeting at which all medical staff of the involved area, i e physicians and nurses, were gathered for an informal lecture about the situation regarding high blood pressure in the county At this meeting it was discussed how the situation might be improved a working group was created and its tasks were set up (Table I) The first task was to work out guidelines for the detection diagnosis, treatment and follow up of hypertensive patients in the County of Skaraborg This work was performed in close contact with representatives for the different categories of medical personnel involved The programme was later officially accepted by vote by the Medical Board of Skaraborg County Council

The realization of the programme

Owing to lacking financial resources and to make an evaluation possible the county was divided into two halves both with around 140 000 inhabitants (Fig 1) The care programme is carried out in one part, the study area, but not in the other the

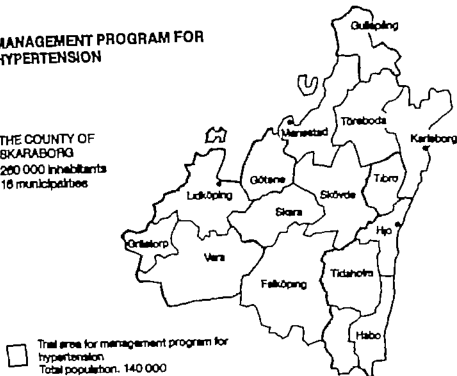


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Table I Structure and responsibilities of the central hypertension unit.

1 *Structure*

A) Chief cardiologist at the central hospital and chief physician at the department of preventive medicine.

B) One district physician.

C) One physician from the department of medicine

D) Two nurses

2. *Definition of duties*

A) *To design the hypertension care programme*

B) Continual follow-up of medical progress and revision of the care programme

C) Training of personnel.

D) Coordination of hypertension care in the County

E) Collection of data.

F) Processing of data

G) To guarantee management of referred hypertensive patients with complications

The working out of the care programme

This started with a meeting at which all medical staff of the involved area, i.e. physicians and nurses were gathered for an informal lecture about the situation regarding high blood pressure in the county At this meeting it was discussed how the situation might be improved a working group was created and its tasks were set up (Table I) The first task was to work out guidelines for the detection, diagnosis, treatment, and follow-up of hypertensive patients in the County of Skaraborg This work was performed in close contact with representatives for the different categories of medical personnel involved The programme was later officially accepted by vote by the Medical Board of Skaraborg County Council.

The realization of the programme

Owing to lacking financial resources and to make an evaluation possible the county was divided into two halves both with around 140 000 inhabitants (Fig 1) The care programme is carried out in one part, the study area, but not in the other the

Treatment is started with either a diuretic or with a beta-receptor blocking agent. The first drug of choice has been left to the physician in charge of the patient, as no valid proof of the superiority of one of the two drugs over the other could be found. If normotension is not obtained with the first drug the alternative drug of the two mentioned above, is instituted. If a normal blood pressure cannot be obtained with this combination, hydralazine will be added. Patients resistant to this triple drug combination will be referred to the central hypertension clinic for evaluation and treatment.

After the institution of therapy the patients are followed-up at intervals that are determined by the severity of the disease and by the response to the given treatment. Yearly controls including history taking, physical examination and some simple laboratory tests are done. Both at these yearly follow-ups and at the initial investigations, special record forms precoded for direct punching and computerization were used. A copy of the record forms is sent to the organizing centre.

Evaluation

An initial baseline survey performed before the programme was started, showed that the study area and the control area were comparable with regard to frequency and severity of hypertension, prevalence of cardiovascular diseases, and socio-economic variables. The evaluation will try to answer the following questions:

Will the programme be:

1. Feasible in the way it is outlined?
2. Effective in preventing or postponing hypertensive complications?
3. Defensible from humanitarian point of view (i.e. to what extent will reduced suffering from reduced morbidity and mortality outweigh any harmful effects of the programme)?
4. Defensible from an economic point of view (i.e. to what extent will any economic gains from reduced morbidity and mortality make up for the costs of the programme)?

The last two points of the evaluation programme will not be discussed here as the outline for these analyses are not yet finished.

The first point of evaluation, i.e. whether it is feasible to carry out the programme the way it is outlined should be answered already during the first two years of the programme. If the majority of the physicians in the study area can be persuaded to follow the programme that is if they detect, diagnose, treat and follow-up hypertensive patients according to the programme, then it can be said that it was feasible to carry out the programme. The problem will be to find out whether the physicians in the study area really follow the intended protocol

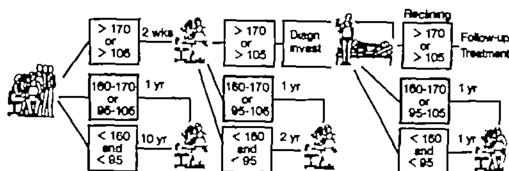
Whether patients with hypertension will be examined, treated and followed up in accordance with the programme, will be followed by checking the copy of the file which is sent to the central unit. These records contain data on the diagnostic work-up, blood pressure during follow-up, frequency of side effects, and frequency of and reason for drop-out. These data are necessary for judging whether the programme can be carried out as intended.

The medical effectiveness will be evaluated by combining two methods. All death certificates for both the study and the control areas will be collected continually. The cause of death will be coded by a person who is unaware of the group to which the certificate belongs. Total death rates and specific causes can then be compared between the two areas. Non-fatal strokes and myocardial infarctions will be followed in both areas by means of a simple stroke and infarction register. The medical effectiveness will then be calculated as the difference in incidence of these terminal points between the study and control areas.

Care programmes of the kind described here are in progress for several other diseases such as diabetes mellitus and breast cancer. A care programme will, for obvious reasons, impose great changes in our present work. It is therefore important for these programmes to be properly evalu-

CRITERIA FOR CONTINUED FOLLOW UP AND DIAGNOSTIC INVESTIGATION

Age 40-60 years



Under 40 years and over 60 years

	Too high	Borderline	Normal
> 60 year	> 180 or > 110	170-180 or 105-110	< 170 and < 105
< 40 year	> 160 or > 95	155-160 or 90-95	< 155 and < 90

Fig 2 Blood pressure limits for different age groups and suggested lines for continued follow-up.

2 weeks Those who still have pressure above these limits are examined according to a standardized diagnostic work up If they still are "hypertensive" they are put on antihypertensive treatment and followed-up The proposed management for other blood pressure categories is shown in Fig 2. The limits for normal pressure shown in Fig 2 also indicate the values to which increased blood pressure should be reduced.

The diagnostic work up includes blood pressure measurement history taking and a physical examination ECG and some simple laboratory tests (Table II) In certain cases but not as a rule X-ray of the heart, intravenous pyelography or isotope renography might be performed

Hypertensive subjects with hypertensive organ involvement such as left ventricular hypertrophy cardiac enlargement, albuminuria or increased S-creatinine will be treated as well as subjects with three blood pressure measurements above the criteria for hypertension Persons with borderline blood pressure elevations might be given treatment if the physician finds that other factors such as serum lipids and family history might worsen the prognosis of the patient

Information to the patient is given both by the physicians and the nurses A special pamphlet with advice to patients with high blood pressure has been worked out

Table II Basic investigation.

Medical history
Physical examination
ECG
Laboratory test (S-electrolytes S-creatinine, S-cholesterol, S-urate; urinary test for albuminuria and glucosuria)

Drug of First Choice in Mild and Moderate Essential Hypertension Clinical Hemodynamic and Economic Aspects

PER LUND-JOHANSEN
From the Medical Department A,
University of Bergen, Norway

At what stage in the hypertensive process drug therapy should be started and which drug should be given the first choice is still uncertain. Conventional clinical trials with a treatment group and a control group are very difficult to use, because the well known clinical complications develop so late in mild and moderate essential hypertension. The largest trials until now the Veterans Administration Cooperative Study Group on antihypertensive agents (12) and the US Public Health Service Hospitals Study (10), were mainly based on thiazide diuretics plus reserpine. Although both studies demonstrated no significant benefit from therapy on myocardial infarction, both studies reported less left ventricular hypertrophy in the treated group compared to the controls.

Animal experiments have demonstrated that in several types of hypertension, a gradual restructuring of the high pressure compartments appears very early when the blood pressure is raised (1). Drug intervention in the pre-hypertensive phase has prevented these changes (2).

In man with essential hypertension the earliest changes in the heart and in the resistance vessels are less well known and biopsy studies are lacking for obvious reasons. Functional studies on the central hemodynamics at rest and during exercise may however tell more than conventional clinical studies. In a follow-up study of the central hemodynamics in 28 subjects below the age of 40 years left untreated over a period of 10 years, it was shown that although no complications could be demonstrated by conventional clinical methods (clinical examination, ECG, ophthalmoscopy urine examination) the stroke volume had decreased and the total peripheral resistance had increased more than was expected from aging alone. (8 9).

In 8 of these subjects the blood pressure had increased (the mean arterial pressure at rest sitting from 116 mmHg to 125 mmHg), and further observation was found unethical. Drug treatment with a *non-cardioselective beta-blocker* bunitrolol, was started. The blood pressure decreased in all subjects. After one year on the beta-blocker the hemodynamic study was repeated. The mean arterial pressure at rest sitting decreased from 125 mmHg to 108 mmHg (13%) but there was no normalization in the central hemodynamics. The total peripheral resistance rose further (10%) and the cardiac index decreased (22%) (Fig. 1)

Studies during exercise demonstrated a marked decrease in the heart rate and in the cardiac index, no compensatory increase in the stroke volume and an increase in the calculated total peripheral resistance, changes resembling those seen by the use of other non-cardioselective beta-blockers (6). Thus, although the beta-blocker had decreased the blood pressure, central hemodynamics were not changed in a normal direction.

Another study demonstrated that during prolonged beta-blocker therapy over 3 years, there was no further normalization of the central hemodynamics, but on the other hand, no further increase in the total peripheral resistance or decrease in the cardiac index. Studies on a *cardioselective beta-blocker* atenolol, showed slightly more favourable changes (7).

ated before they are promoted to definite diagnostic and therapeutic moulds for a whole country We have found it necessary to evaluate the feasibility as well as the medical effectiveness and humanitarian and economic defensibility For other diseases where there is full agreement on how the disease should be treated it will be possible to make the evaluation easier by excluding evaluation of the medical effective ness Unfortunately it is still valid for many major diseases that opinions is divided regarding the value of different forms of treatment. When this is the case evaluation of the medical effectiveness remains most important.

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Discussion.

Puska

The programme applies primarily to hypertension but it will also apply to other risk factors It is not only a matter of primary prevention but also of secondary prevention Is it possible to evaluate the effect of this?

Berglund.

We will probably not be able to separate the effect of hypertension treatment and the effect on the treatment of other risk factors which, without doubt, will be better in the intervention area than in the control area

Puska.

How will you make sure that the registration of myocardial infarction and apoplexy is comparable in the intervention and control areas?

Berglund

We will not have the opportunity of letting one doctor make the diagnosis by visiting all hospitals and examining every single patient, but we have agreed on common diagnostic criteria, which are found in writing at every clinic in the area. The validity of the register will be evaluated in smaller groups of patients

As regards comparison between the intervention and control areas we have already carried out a base-line survey on a sub-sample comprising 8% in both areas in order to verify that they were comparable with regard to cardio-vascular mortality and morbidity and blood pressure. We also intend to conclude with a terminal survey to determine if the changes in these important factors are the same in the two areas in 7 years time when the programme will finally be evaluated.

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Discussion:

Hidén.

I feel that the hemodynamic considerations Lund-Johansen has presented here are perhaps little too sharp. Others, at least, have found that the primary rise in peripheral resistance decreases with beta-blockers. As for diuretics, you yourself have found a decreased cardiac output in certain situations, so one cannot just say that diuretics only affect the peripheral resistance. It may be rather by chance that one drug is used first instead of the other because in many cases, perhaps almost all, a combination of a diuretic and a beta-blocker will be used in the end.

Lund-Johansen.

There is some misunderstanding about the effect of beta-blockers on vascular resistance. Trials with propranolol in patients who had been examined before treatment, after acute administration and then after some months treatment have shown that vascular resistance rises acutely then gradually decreases and ends at about the same level as it was before treatment. Consequently due to the rise in the vascular resistance immediately after treatment is started and when the cardiac output is decreased, there is little effect on the blood pressure Gradually as time passes, the vascular resistance is decreased but levels lower than the starting point are rarely obtained. The cardiac output remains reduced about 15%

I believe there is a fundamental difference in the circulation of individuals on long term thiazide treatment and individuals on long term beta-blocker treatment. There is a great difference in the pulse frequency because diuretics do not affect the pulse frequency either resting or during physical exercise, while beta-blockers induce a drastic reduction. All the five beta-blockers I have investigated induce a fall in the cardiac output, and during physical exercise in particular it is considerably lower than normal I am surprised that individuals tolerate it as well as they seem to do but I would not be surprised if future investigations show that a hypokinetic circulation like this may prove unfortunate. Therefore, the effect of these drugs on the circulation is quite different. But on the other hand by using diuretics we introduce electrolyte changes, changes in the uric acid and carbohydrate metabolism. The plasma volume is also changed and will remain decreased during long term therapy about 7%

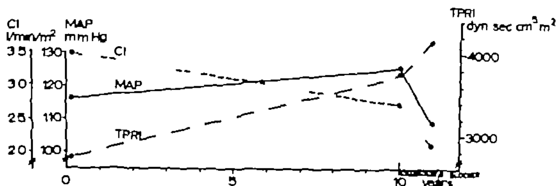


Fig. 1 Cardiac index (CI) mean arterial pressure (MAP) total peripheral resistance index (TPRI) during 10 years without treatment followed by 1 year on beta-blocker (bunitrolol) n = 8 Sitting Position rest.

The *thiazide diuretics* induce a different hemodynamic pattern reduction in the total peripheral resistance without changes in the heart rate or stroke volume during exercise (4) In a group of 6 patients between 40 and 49 years old when first studied and treated with a thiazide as a sole drug during ten years the blood pressure decreased from 134 mmHg to 103 mmHg (23%) Although there was some decrease in the cardiac index over ten years there was no further increase in the total peripheral resistance in contrast to a similar group of patients left untreated for ten years Thus the thiazides seem to induce a decrease in total peripheral resistance during the first year of treatment, and from then on no significant increase over the next decade.

The more recent antihypertensive agent *prazosin* induces a different hemodynamic pattern a marked decrease in the total peripheral resistance, an increase in the stroke volume and cardiac index at rest as well as during exercise Thus this drug induces a normalization of the central hemodynamics over a period of one year More prolonged studies are lacking (5)

The *side-effects* of the three types of drugs, the thiazides the beta-blockers and prazosin are well known and usually acceptable, when the conventional contraindications are respected.

There are large differences between these three types of drugs when the economy is taken into consideration The thiazide diuretics are much cheaper than the beta blockers and prazosin. The price for one year's treatment with a conventional thiazide preparation will be about 200 Norwegian kroner (N Kr), with a conventional cardioselective beta-blocker N Kr 1,200 and with prazosin about N Kr 700 per patient

Thus the thiazides may still defend their position as the drug of first choice in mild and moderate hypertension. Prazosin with very promising hemodynamic characteristics has still been used for too short a time to allow a definite conclusion with respect to its position as a possible drug of first choice.

With respect to the beta blockers it should be emphasized that death from myocardial infarction or a malignant arrhythmia *is the greatest threat for patients* with mild and moderate hypertension It is possible that beta blockers may protect against these lethal complications (3 11) If this is going to be documented in further studies, it is likely that the beta blockers will definitely replace the thiazides as the drug of first choice It is even possible that the anti-arrhythmic effect might be more important than the blood pressure lowering effect in this type of patient

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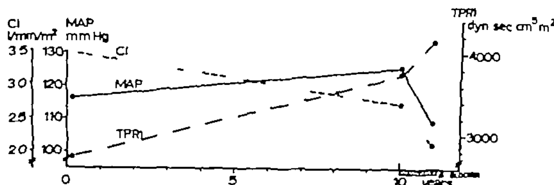


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The Organisation of Treatment of Hypertension the Role of the General Practitioner

SIGURD HUMERFELT
From the Institute of General Practice,
University of Bergen, Norway

The majority of hypertensive patients in Norway are taken care of by the general practitioner (GP). However we know very little in what way these patients are screened, treated and followed-up in practice

The following problems arise:

Which diagnostic procedures are used by the GP?

How many are taken care of by the GP without consulting a specialist or a hospital?

Which are the criteria for referral?

How are the follow-up routines?

How does the GP evaluate the effectiveness of the treatment?

1. Standardization of methodology

At our institute we have felt the need for a standardized technique. This applies to several of the postgraduate training programmes. These programmes are built on.

a. A video-tape on diagnostic procedures and recommendations for therapy

b. A pamphlet "Hypertension in General Practice" presenting the most important clues of the diagnostic, therapeutic and follow up procedures.

c. Introduction programmes on the measurement of BP and on the technique of ophthalmoscopy adapted by Professor J.A. Osterhuis, Leyden.

These programmes have been presented at several courses for practitioners.

2. The contribution of the GP in hypertension surveys and therapeutic controls

During the last 5-6 years the need for studies on hypertensives under the supervision of the GP has been realized, especially in our country with a system of decentralized health service.

Some examples.

1. The Peripress treatment survey. This drug was primarily accepted for the use of specialists only because of the initial side effects. Further studies were initiated to investigate these first-dose phenomena. Several groups of GP's (totally 142) joined in a cooperative study. Based upon these results of a low initial dosage programme, this drug is now available for general prescription.

2. Several other surveys are in the hands of GP's. The intervention programme, initiated by the State Mass X-ray Department in the County of Finnmark in Sogn and Fjordane. After a screening programme all hypertensives are regularly followed-up and treated by the district doctors and GP's.

3. A cooperative study initiated by the Institute of General Practice in Oslo, the Section of Clinical Pharmacology and Toxicology at Ullevål Hospital, the Directory of Health, and the Institute of Pharmacotherapy University of Oslo, has recently taken place in two counties in Norway

   The main aim of this investigation was to study more closely the GP's methods of screening and treatment and their follow up routines. In all, 154 GP's have taken part in this comprehensive survey

Discussion:

Holte:

As a general practitioner interested in hypertension, I have the impression that the treatment and check-up of hypertension is poor. What is the reason for this? Is it because the doctor lacks information? or the

Wilhelmsen

I would also question the possible effect of beta blockers direct on the heart. We have still not been able to prove such an effect in the treatment of hypertension, but I would mention that at present a multi centre study is being carried out here in Scandinavia, conducted from Gothenburg Several centres are involved, for example Karelia, other groups in Sweden and groups in Iceland We need many patients to be able to show the difference in mortal ity between the two drug choices We have estimated that we need about 4 000 pa tients and at the moment there are only about 1 000

Doctor Patient Relationship in Long term Treatment of Hypertension

H. STORM-MATHISEN and K. HEBNES
From the Deaconess Hospital Lovisenberg,
Oslo, Norway

There are many different ways of evaluating a doctor-patient relationship and compliance with a therapeutic regimen. One obvious way is to measure the serum level of the prescribed drug or the urine excretion of the metabolites (1). These methods can only be used in a limited number of patients and for a relatively short observation time. The tablet counting is more convenient in the long-term treatment.

Also an interview might lead to better doctor-patient relationship and seems to be a fairly adequate method for evaluating patient compliance (2, 3).

An indicator of the compliance to therapy over the years in treatment of a chronic disorder like hypertension is probably to study the number of drop-outs from follow-up (4 5)

In the Deaconess Hospital (Lovisenberg sykehus), Oslo we have in collaboration with several general practitioners treated and checked-up thousands of hypertensive patients. In the period 1955-1975 we have registered 745 patients under our own treatment for a minimum f one year and in the mean more than 10 years.

After 1965 this method has been followed.

1. The patient is called with a letter to a policlinic interview and investigation at a given date and time. The waiting time is not more than few minutes. The laboratory study is done at the same time.
2. The patients are examined about twice a year or more if necessary The examination by the physician lasts for about half an hour The patient's use of tablets is checked on these occasions and side effects are discussed. Also the other parts of the regimen, smoking, diet, etc. are discussed. Blood pressure is measured in sitting and standing position, and standing after five knee bendings
3. Reports and results concerning laboratory findings are given in a letter to the patient together with a written message about the new dosage of tablets and the new appointment day and hour The most convenient time for this has already been discussed during the consultation.
4. Blood pressures are plotted on millimetre paper size 21 x 29 cm (A4). The notes for many years are collected in a loose leaf book after a system with cues' Methyldopa, beta-blocker spironolactone etc. according to the leading drug treatment.
5. Address-cards with cues are collected in special boxes. The main register has signals for cross reference given to this special hypertension register

Results of compliance (drop-out) from 1 1.65 1 10 77 (Table I): 192 patients (124 men and 68 women) who began treatment during the period 1965-70 were investigated: I this material we had 10 drop-outs with unknown destiny

Six of these had been treated by other physicians on the hospital staff We had 4 drop-outs of patients treated by ourselves, 1 after one year 1 after two years, 1 after three years and 1 after four years of treatment before satisfactory blood pressure values were attained. Side-effects such as values were attained. Side-effects such as impotence and feeling uncomfortable led patients to stop treatment in these cases. In 3 patients treatment could be stopped because the blood pressure remained nor

has failed to make up his mind on hyper tension questions? If the latter is the case how can it be remedied? Perhaps practi tioners ought to take part in the research and help in the development of research projects

Humerfeldt

I quite agree with Holte s point of view The four institutes in Norway who are working on the primary health service problems have also collaborated on a research committee

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4 Blood pressures are plotted on millimetre paper size 21 x 29 cm (A4). The notes for many years are collected in a loose leaf book after a system with cues Methyldopa, beta-blocker spironolactone etc. according to the leading drug treatment.

5 Address-cards with cues are collected in special boxes. The main register has signals for cross reference given to this special hypertension register

Results of compliance (drop-out) from 1 1 65 1 10 77 (Table I)· 192 patients (124 men and 68 women) who began treatment during the period 1965-70 were investigated. In this material we had 10 *drop-outs with* unknown destiny

Six of these had been treated by other physicians on the hospital staff We had 4 drop-outs of patients treated by ourselves, 1 after one year 1 after two years, 1 after three years and 1 after four years of treatment before satisfactory blood pressure values were attained. Side-effects such as values were attained. Side-effects such as impotence and feeling uncomfortable led patients to stop treatment in these cases. In 3 patients treatment could be stopped because the blood pressure remained nor

Table I Patient compliance in long-term antihypertensive treatment.

Drop-out study 1 1 65 1 1 70 — 192 patients (124 men 68 women)						
	Non-compliance		Treatment stopped	Changed address and doctor		
per 1 10 77	Unknown	Treatment stopped Not improved	Improved	Compliance	non-comp	Total
Men	4(+4)	4(+0)	1	17	4	34
Women	0(+2)	0(+2)	2	7	0	13
Total	*4(+6)*	*4(+2)*	*3*	*24*	*4*	*47*

The treatment has been started in the period from 1 1 65 to 1 1 70
The patients have been followed up until 1 10 77

Figures in brackets indicate patients treated by associated doctors.

mal for several years without drugs. Twenty-eight patients left the district and changed physicians Of these patients 24 had regular appointments with the new physician. Only 4 of them dropped out of treatment The non-compliance rate for the given period 1965 1977 was found to be roughly *10% or roughly 1% per year*

We found it most important to shorten the waiting time in connection with check up consultations and the taking of blood for investigation. The waiting-room and the office are given a pleasant appearance The appointments are given by mail but flexible and most convenient for the patient In Oslo we have a relatively steady population without too much moving which is favourable for this type of study We feel that the best method for increasing compliance is to combine treatment with teaching and small discussions about hypertension and other problems concerning health and well being. Our policy has always been to inform the patients about the results of blood pressure measurements and laboratory findings We have found that only in this way are we able to keep our patients as collaborators in our attempts to control their hypertension

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Proceedings of SYMPOSIUM ON ECHOCARDIOGRAPHY

Lund, Sweden
May 13–14, 1977

Edited by
Arne Gustafson and Stig Persson

Distributed by The Almqvist & Wiksell Periodical Company Stockholm, Sweden

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In 1953 Inge Edler and Hellmuth Hertz started their pioneer work resulting in the paper The use of ultrasonic reflectoscope for the continuous recording of movements of the heart walls in the proceedings of Kungliga Fysiografiska Sällskapet in Lund in 1954 At that time these two scientists could hardly anticipate that they had given birth to a method of investigation which would turn out to be of an almost revolutionizing importance for the examination of patients with heart disease

After an initial period when the method was mainly used for diagnosing mitral valve stenosis and pericardial effusion echocardiography was become widely used in the morphological and functional evaluation of most heart diseases Only by use of echocardiography we have possibilities to estimate the real frequency of diseases as idiopathic hypertrophic subaortic stenosis and prolaps of the mitral valve

The importance of echocardiography is also clear from the fact that its different methods of application have captured a rapidly growing part of cardiological literature during the last decade During this period an important technical development has taken place above all the introduction of two-dimensional echocardiography which has enlarged the possibilities of investigating the anathomy and function of the heart

This symposium was arranged as a mark of honour to Inge Edler at his retirement from the appointment as head of the Cardiological Clinic at the University Hospital of Lund It was intended to give an understanding of the place of echocardiography to-day and its possibilities of development in the future

SYMPOSIUM ON CONGENITAL HEART DISEASE

FREE COMMUNICATIONS

CONTENTS

SYMPOSIUM ON CONGENITAL HEART DISEASE

FREE COMMUNICATIONS

PRINCIPLES OF TWO-DIMENSIONAL REAL TIME ECHOCARDIOGRAPHY IMAGING

P R GOLDBERG

From the Biomedical Research and Development Smith-Kline Instruments Sunnyvale California.

INTRODUCTION

Two-dimensional ultrasonic imaging has developed over the past two decades from a research tool into a viable diagnostic modality Though the use of this technique for cardiac imaging is relatively new a large number of devices have been developed for the expressed purpose of performing this task Since ultrasonic images can be derived by many different methods these instruments are not all based on the same physical principles For an echocardiographic visualization system to provide the greatest diagnostic utility it must employ concepts which are dictated by the clinical need It is the purpose of this discussion to start with basic clinical needs and ultrasonic imaging physical principles and describe in steps the development of a two-dimensional real time ultrasonic visualization system ideally suited for cardiac imaging

1 0 BASIC CLINICAL NEEDS

All medical diagnostic instrumentation has been created for the same purpose that is to provide the clinician with detailed information directly related to the condition of the internal organs of the body An echocardiographic imaging system performs this task by utilizing ultrasonic energy to form a two-dimensional image of the structures of the heart What characteristics should this image possess if it is to be of maximum diagnostic utility? On the surface this appears to be a simple question with one answer The image displayed should be a distortion free representation of the cardiac structures

Without a doubt the display on non-distorted cardiac images is the goal of all ultrasonic visualization systems However there are significant impediments to the realization of this ideal From a clinical standpoint the visualization system must capture the details of a rapidly moving object through an echocardiographic "window" which varies greatly in size from patient to patient As stated by Dr Harvey Feigenbaum in the second edition

of his book entitled Echocardiography published by Lea & Febiger sound travels poorly through a gaseous medium such as air It is not possible for ultrasound to traverse any significant amount of lung tissue and still obtain adequate echoes from the heart The acoustic mismatches between bone and soft tissue is great If one tries to direct the sonic beam through bone almost all of the ultrasonic energy is reflected or absorbed Thus an echocardiographic examination is impractical if the transducer is placed over the sternum or rib This problem may not be as great with infants or young children since the ribs and even sternum may not be calcified However in adults one is limited as to how the echocardiographic examination is performed with respect to transducer placement The usual echocardiographic window" is between the second and fifth intercostal spaces within 3 to 4 cm to the left of the sternal border One can usually examine the heart from at least two or sometimes three interspaces In many adult patients the second interspace has lung overlaying the heart and is a difficult location for the echocardiographic examination In some adults with low diaphragms even the third or fourth interspace might be extremely difficult because of overlaying lung On the other hand in children the higher interspaces are commonly available for the echocardiographic examination and in young infants the transducer can probably be placed right over the sternum and the ribs if necessary

These clinical realitites are the starting point for the development of the perfect two dimensional real time echocardiographic imaging system They indicate that the visualization system of choice will have the following basic characteristics

1 1 The ability to place easily manipulate and angle the imaging transducer within the confines of the limited echocardiographic window

1 2 The ability to display in 2 -dimensions and simultaneously record without distortion the motion and position of the rapidly moving cardiac structures

1 3 The ability to freeze motion thus providing a sharp and clear stop motion two-dimensional picture for diagnosis and measurement

2 0 FUNDAMENTALS

Before one can embark on the development of an instrumentation system two items must be defined The basic characteristics of the system and the method of achieving these characteristics The qualities required for a superior two-dimensional real time cardiac imaging system as delineated in section 1 0 shall serve as the systems guideline The method of choice for this

discussion is pulsed ultrasonic imaging The best implementation of this method can only be ascertained after an analysis of pulsed ultrasound two-dimensional real time imaging fundamentals

In order to obtain images by the use of pulsed ultrasonic energy it is required to transmit brief ultra-high frequency acoustics signals forming an ultrasonic beam followed by a relatively long interval during which no transmission occurs During this time the pulse energy is transmitted through the body Whenever a pulse of energy strikes a boundary between two surface having different acoustic impedances a portion of the energy is reflected some of it returning to the source The remaining portion of the original energy is available to produce additional echos from deeper interfaces The ultrasonic transducer which serves the purpose of both a transmitter and receiver of acoustic signals converts the ultrasonic energy reflected back from the body into electrical signals as they arrive at the transducer s surface This signal is amplified processed and displayed as a single line of ultrasonic information which shows the relative position of tissue interfaces along the axis of the ultrasonic beam The second dimension of the ultrasonic image which will display the spatial orientation and shape of the body structures is established by rapidly scanning the ultrasonic beam along the surface of the body in either a linear or sector pattern A separate electrical signal analogous to the instantaneous position of the scanned ultrasonic beam is processed and utilized to create horizontal and vertical signals which are used to direct the motion of the electron beam of a cathode ray tube such that it coincides with the instantaneous position of the returning ultrasonic beam The resultant image formed from the multi-positioned ultrasonic lines of information is a representation of the internal organs of the body

It is clear from the above discussion that it takes time to form a two-dimensional ultrasonic image The time required is dependent upon the speed of sound in body tissue the depth of body tissue that is to be visualized and the speed at which the ultrasonic beam is scanned across the body

The velocity of sound utilized by the American Institute of Ultrasound in Medicine for the purpose of aligning calibrating and measuring the performance of a *pulsed echo* diagnostic apparatus is 1540 Meters/sec (1) Using this number we find that ultrasound will traverse within the body 1 54 mm every microsecond or in 649 microseconds ultrasound will travel

of his book entitled Echocardiography" published by Lea & Febiger sound travels poorly through a gaseous medium such as air It is not pos sible for ultrasound to traverse any significant amount of lung tissue and still obtain adequate echoes from the heart The acoustic mismatches between bone and soft tissue is great If one tries to direct the sonic beam through bone almost all of the ultrasonic energy is reflected or absorbed Thus an echocardiographic examination is impractical if the transducer is placed over the sternum or rib This problem may not be as great with in fants or young children since the ribs and even sternum may not be calcified However in adults one is limited as to how the echocardiographic examina tion is performed with respect to transducer placement The usual echocardio-graphic "window" is between the second and fifth intercostal spaces within 3 to 4 cm to the left of the sternal border One can usually examine the heart from at least two or sometimes three interspaces In many adult pa tients the second interspace has lung overlaying the heart and is a diffi cult location for the echocardiographic examination In some adults with low diaphragms even the third or fourth interspace might be extremely difficult because of overlaying lung On the other hand in children the higher inter spaces are commonly available for the echocardiographic examination and in young infants the transducer can probably be placed right over the sternum and the ribs if necessary

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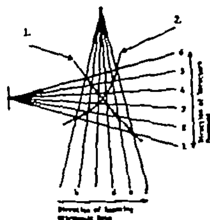


Fig 1 "Moving stick analogy to show distortion. Ef ect due to slow scan rate

1 Shape of displayed structure being visualized by an Ultrasonic Imaging system with a slow scan rate relative to the speed of the structure In this case the structure movement is from top to botton

2 Shape of displayed structure being visualized by an Ultrasonic imaging system with a slow scan rate relative to the speed of the structure In this case the structure movement is from bottom to top

in the real time moving image would be that of an artificial flapping of the structure being visualized

Distortions due to finite acquisition time are not the only two-dimensional ultrasonic image aberrations that can occur It was stated earlier that pulsed ultrasonic energy forms a beam Since this beam has a finite cross sectional dimension and is composed of ultrasonic energy pulses of finite width the body structures will not be displayed with perfect accuracy The effect of pulse width is to increase the apparent thickness of a structure Distortions due to cross sectional beam shape depend on the scanning system employed the degree of beam divergence the distance between the transducer face and the structure being visualized and the intensity of anomalous off-axis beams called side lobes

Fig 2 is a simplified representation of an ultrasonic scanning system which utilized a linear array transducer This transducer is composed of many small transducer elements placed side by side The ultrasonic beam is scanned by firing each one of these transducers sequentially thus causing each subsequent ultrasonic beam to be displaced laterally from the previous beam

As the ultrasonic beam propagates away from the face of the transducer elements it remains essentially collimated for a distance determined by the dimensions of the element and the frequency of the transmitted ultrasonic energy It then begins to diverge The greater the physical dimensions of the element and the higher the ultrasonic frequency employed the longer the near field For a rectangular transducer element the length of the near field in the lateral dimension will not be the same as the length of the near field in the direction orthogonal to the lateral dimension The need for a large number of lateral scanning positions in a linear array scanning system dictates that the lateral dimensions of the transducer elements used must be

through one millimeter of tissue In order to sense the presence of a body structure it is necessary for the acoustic pulse to travel to the interfa ce be reflected and arrive back at the transducer Therefore it requires 1 298 microseconds to visualize a structure one millimeter away from the transducer face

At least 15 centimeters of tissue depth must be displayed for the purpose of adult cardiac imaging This means that each single line of ultrasonic information can be acquired in no less than 194 7 microseconds If we desire to create a two dimensional picture it is required as outlined ear lier to scan the ultrasonic beam across the body The speed at which we scan will determine how many lines of ultrasonic information the final ima ge will contain The slower the scanning speed the more ultrasonic lines in the display

Clearly the final picture will appear smoother if more ultrasonic lines are used What is not so evident is that a slow scan of a rapidly moving structure leads to image distortion

Figure 1 is a simplified representation of a realtime ultrasonic two-dimen sional scanning system in the process of imaging a fast moving cardiac structure such as an aortic valve No attempt has been made in this illustration to properly represent the actual contours of this complex structu re It is assumed that the valve is pivoted on one end and moves as a stiff stick-like formation An imaging device which employes a sector type scan has been chosen only for easy of explanation This discussion applies equally well to a linear scanning system

As can be seen by the schematic representation in fig 1 the structure which is being visualized moves during the time that the ultrasound beam is being scanned across its surface When the scanning beam is in position a the structure is in position 1 At this point in time a dot representing the intersection of the ultrasonic beam and the structure is drawn on the display screen A short time later a dot representing the intersection of beam position b and structure position 2 is drawn on the display screen This process continues until the ultrasonic beam has finished its scan at beam position f and structure position 6 The resultant image is a curved slanted line If the structure direction was from top to bottom instead of from bottom to top the resultant image would again be a curved slanted line but it would be oriented at an angle with respect to the first line The distortion that one would see

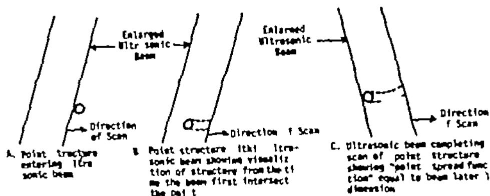


Fig 3 Graphic representation of distortions resulting from beamwidth in a sector scanning imaging system with a collimated beam.

Image uncertainties due to the effect of transducer beam side lobes are most often associated with phased array imaging systems These anamolous off axis beams caused by the limited number of elements that can be practically used to construct a phased array transducer and the unavoidable edge discon tinuities between closely spaced adjacent elements can result in the multip le display of the same structure in different screen locations Image ambi guities may follow if a strongly reflecting target is at the location of the side lobe while a weakly reflecting target is being visualized by the main lobe (9) This phenomenon is schematically represented in fig 4

Three beams are illustrated on this simplified representation one main axis beam and two side lobes When the main axis beam intersects the strong ultra sonic reflecting structure shown the processed reflections from the inter face will properly display the structure as shown in panel A At this ti me the side lobes are not intersecting the formation and therefore only the actual structure is visualized When side lobe A intersects the structure as shown in panel B the main axis is pointing to the right Because the display system is designed to show echos from the main axis beam only the received echos from side lobe A are shown on the right portion of screen The same is true for side lobe B when it intersects the structure only at this time the main axis beam is pointing towards the left thus causing echoes from side lobe B to be shown on the left Panel D" shows the com posite image resulting from the main beam and the two sides lobes It should be noted that real side lobes are typically wider than the main beam and that the phantom images will therefore be less distinct bur smeared over more area than the real image

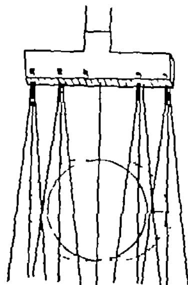


Fig 2 Distortion caused by linear scanning array Beam width

relatively small This leads to a short near fiel and a rapidly diverging series of scanned ultra sonic beams Image distortions due to these spreading beams are schematically represented in fig 2 Points on the circular structure visua lized by the off-axis ultrasonic energy intersec ting the structure being viewed appear on the ultrasonic image as if they were shifted up or down onto the beam s main axis from their actual positions (5) This leads to an oval repre•enta tion of the circular structure In reality this simplified diagram does not indicate all the dis tortions produced by the diverging ultrasonic beams Multiple intersections by various portions of the non collimated beam have not been shown for clarity It should be noted that it is common practice to fire groups of transducer elements together in an attempt to collimate the beams

Beam width affects images produced by an ultrasonic visualization device which employs a sector-shaped scan in a different manner than that described for a linear scanning system In the case of the "mechanical sector scanning system as well as the phased array" scanning system lateral beam dimen sions cause individual points on a structure to be mapped into curved lines on the final displayed image Fig 3 shows this phenomenon graphically
As the ultrasonic beam passes over the point being visualized an ultrasonic echo is produced This echo continues to be exhibited for as long as the point is within the confines of the passing ultrasonic beam The image thus produced will be a curved line which begins when the structure first enters the ultrasonic beam and ends when the lateral dimension of the ultrasonic beam no longer intersects the point This misrepresentation is minimized for a mechanical sector scanner system by using a transducer of sufficient diameter to allow the existance of a relatively lengthy near field zone and by the use of acoustic lenses in front of the transducer element to further collimate the beam This will cause the structure to be illuminated by a parallel con verging or slowly diverging ultrasonic beam for most of the image depth thus limiting the image point spread function to approximately the diameter of the transducer element utilized Some phased array scanning systems utilize elect ronic focusing means to minimize this problem (8)

higher frequencies result in greater ultrasonic attenuation within the body thus placing a limitation of tissue depth penetration A practical system must therefore have a relatively large transducer This large transducer requires an acoustic window which frequently may be larger than is available With respect to adult cardiac patients this problem is especially true The transducer will of necessity cross the ribs and in adults these structures are frequently calcified thus causing an image distortion In addition one does not have the ability to angle the transducer in the long axis (2) Clearly the transducer would lift off the patient s chest causing a loss of image

For cardiac use the transducer associated with a phased array imaging system does not display the size limitations of the transducer associated with the linear array imaging system Phased array transducers which are 23 mm in length and 14 mm in width (the width dimension corresponds to the elevation dimension of each of the transducer elements) are in present use (7) However there still remains a problem associated with transducer angulation and acoustic window restrictions For a phased array transducer to give best results it is necessary for all of the elements of the transducer to be in intimate contact with the patient s chest The phased array transducer being a rigid structure will lift partially off the skin surface in the process of angling the transducer in the long axis direction A degraded image will result In addition because the beams from all of the elements contained within a phased array transducer are required in order to scan or focus the beam any beam obstruction caused by calcified ribs for example will produce image distortions

At the present time the transducer associated with the mechanical sector scanner imaging system represents the best overall combination of qualities Because it uses a transducer with a small single ultrasonic element (current models utilize elements which are 12 7 mm in diameter) the mechanical sector scanner probe is easy to place manipulate and angle within the confines of the echocardiographic window The small diameter of the ultrasonic element allows unobstructed placement between adult ribs and maintenance of contact with the chest surface during procedures which require transducer angulation In addition the mechanical system offers a great deal of flexibility with respect to specialized transducer configurations The transducers most commonly associated with a mechanical sector scanner are ones in which the transducer element oscillates on the skin through an angle of from 30 to 60 degrees When a transducer with a 30 degree angle is employed the vibratory

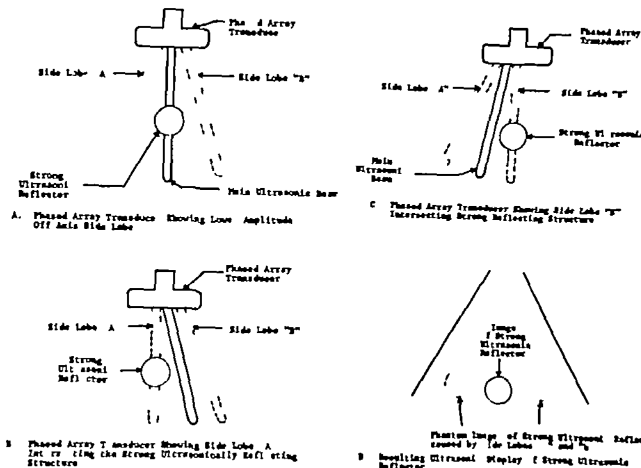


Fig 4 Visualization of a strong ultrasonic reflector by an imaging system with sides lobes

3 0 THE ECHOCARDIOGRAPHIC TRANSDUCER

After an analysis of two-dimensional real time ultrasonic imaging fundamentals has been completed one can continue to pursue the development of a cardiac imaging system based on this technology As was pointed out in section 1 one of the three basic characteristics of the cardiac visualization system of choice is that the transducer utilized by the system will be easy to place manipulate and angle within the confines of the limited echocardiographic window The trans ducer associated with the linear array scanning system because of the need to have many transducer elements side by side in order to obtain a sufficient num ber of ultrasonic lines of information in a linear scanning formation must be in the form of a straight bar This bar (see fig 2) will vary in size depending on the acceptable ultrasonic line density distortion resolution and operating frequency As pointed out earlier all of these qualities are interrelated The smaller the transducer element the poorer the resolution and the greater the distortion The higher the ultrasonic frequency the better the resolution and the less the distortion However in this case a penalty is paid in that

higher frequencies result in greater ultrasonic attenuation within the body thus placing a limitation of tissue depth penetration A practical system must therefore have a relatively large transducer This large transducer requires an acoustic window which frequently may be larger than is available With respect to adult cardiac patients this problem is especially true The transducer will of necessity cross the ribs and in adults these structures are frequently calcified thus causing an image distortion In addition one does not have the ability to angle the transducer in the long axis (2) Clearly the transducer would lift off the patient s chest causing a loss of image

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sensation on the patient s skin can be made relatively small with proper transducer manipulation Devices of this nature have been used on neonates which were only several days old, with success (6) As the angle increases however the vibratory sensation becomes a greater and greater problem

A hand held mechanical transducer has been suggested which utilizes a rotating transducer element system totally immersed in an acoustically transparent fluid and which is sealed within an acoustically transparent housing (4) This configuration will totally eliminate any vibratory sensation and simultaneously expand the transducer s angle of view to 90 degrees

4 0 ECHOCARDIOGRAPHIC IMAGE DISPLAY TECHNIQUES

All two dimensional imaging systems, whether they are based on linear scanning mechanical scanning or phased array scanning principles must use electronic display techniques in order to place the ultrasonic image on a screen There are numerous methods for performing this task However the second and third basic requirements of an imaging system especially designed for cardiac diagnosis limits our selection As outlined in section 1 the imaging system of choice will have the ability to display in two-dimensions and simultaneously record without distortion the motion and position of the rapidly moving cardiac structures It will also be able to freeze this motion and thus provide a sharp clear stop motion two dimensional picture for diagnosis and measurement

As discussed in section 2 the original data which is used to create an ultrasonic image is in the form of ultrasonic lines of information These lines of information form an image when they are drawn on a cathode-ray tube screen in synchronism with the instantaneous position of the ultrasonic beam This is the basic function of an ultrasonic imaging system regardless of the beam scanning mechanism employed However if a system is to meet the strict echocardiographic requirements delineated above the format utilized to draw the ultrasonic lines of information on the cathode ray tube screen must be carefully chosen

The scanning format utilized must be compatible with the manner in which the ultrasonic beam is being swept across the body In case of the linear array system the ultrasonic lines of information are perpendicular to the direction of the scan Therefore the display format for this type of system would consist of horizontal lines which are drawn on the screen parallel to

one another in the form of a rectangle For a system which employs a sector scan the lines of ultrasonic information would be distributed in a radial pattern The format for this system would be composed of lines lying on the radii of a triangular shaped sector The format however is not completely defined until the field rate frame rate and interlaced scanning ratio have been determined These specifications are the ones which effect the system s motion visualization capability the most

Interlaced scanning is a method of image formation on the screen of a cathode ray tube in which the image is composed of two or more parts laid down sequentially in two or more sets of lines The first set of lines which forms the first part of the image is drawn on the screen followed by the interleaved placement of one or more additional sets of lines which form the remaining portions of the image Each individual set of lines is called a field The composite of all of the image parts which make up the whole image is called a frame In a non-interlaced scanning system the whole image is formed by one set of scan lines Therefore a field equals a frame which equals the whole non-interlaced image Hence the term field has no meaning with respect to this scanning arrangement

It has been clinically determined that an echocardiographic system which employs an interlaced scanning method with a field rate of 60 fields per second adequately stops cardiac valvular motion in most cases The faster the field rate the better especially in the case of valvular studies (3) However there is a practical limit to the field rate a system can utilize By using the time that is required to acquire echo information from a depth of 15 centimeters of tissue which was calculated in section 2 194 7 microseconds plus the time needed to assure that echos from structures deeper than 15 centimeters are attenuated sufficiently so that they will not mix with the near field echos from the subsequent pulse 65 microseconds and dividing this number into the time that is allotted to draw a crisp cardiac image 16 7 milliseconds

($\frac{1}{\text{60 fields per second}}$ 16 7 milliseconds per field) it is found that the maximum number of ultrasonic lines that can be displayed in a field which provides adequate valvular motion rendition is 64 3 lines

$$\left[\frac{\text{16.7 milliseconds per field}}{\text{194 7 microseconds per ultrasonic line + 65 microseconds}} \quad \text{64 3 ultrasonic lines per field}\right]$$

For a non interlaced scanning format the number calculated above indicates that the final image visualized by the viewer will be composed of a maximum of 64 3 ultrasonic lines of data This is not the case for an interlaced scanning format Due to the persistance associated with the viewer s vision a frame which is composed of two interlaced fields will appear to have twice this, number of ultrasonic data lines or a total of 128 6 lines Ta king this concept further and utilizing a frame composed of four interlaced fields an image will be produced which appears to contain 257 2 ultrasonic data lines

This technique does more than just fool the eye into believing that the picture on the screen is made up of a great number of lines it also alters the distortion produced by motion of the cardiac structures The motion dis tortion schematically illustrated by fig 1 (the "moving stick analogy") app- lies to either the fields of an interlaced system or the frames of a non in terlaced system It indicates that attempting to increase the number of ult rasonic data lines in an interlaced field or a non interlaced frame by redu cing the transducer s scanning rate will produce a moving image with an arti ficial flapping artifact Fig 5 illustrates an interlaced scanning system with a four field to one frame interlacing format and a field rate of 60 fields per second Field 1 is shown scanning across the structure being visu alized in 16 7 milliseconds a scanning speed which is fast relative to the speed of the structure This allows the "moving stick to be shown as a straight line in the display Field 2 scans at the same rate as field 1 thus the moving stick visualized by field 2 is in a slightly lower position than the moving stick visualized by field 1 The same is true for fields 3 and 4

Since the ultrasonic image is formed by the echos created by the intersection of the ultrasonic beam and the structure being visualized the interlaced fra me will show a series of points which have been acquired during the total frame time of 66 8 milliseconds (16 7 milliseconds x 4 = 66 8 milliseconds) The points produced by field 1 will be displaced from the points produced by field 2 The points produced by each field will be displaced from the points produced by the previous field in either an upward or downward direc tion depending on the direction of the structure being visualized Fig 5 in dicates that a saw tooth image abberation is produced when the structure moves downward The dots descend until the next ultrasonic line from field 1 is

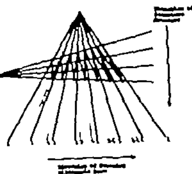


Fig 6: "Moving stick analogy to show motion artifact caused by an interlaced scanning system with a four field to one frame scanning ratio

drawn and then they reset to the position of the "moving stick at the time of the field 1 scan The slower the structure being imaged the smal ler the saw tooth distortion Unlike the bending and flapping image abberations caused by a field rate which is slow as compared to the speed of the cardiac structures the sawtooth distortion can be easily seen for what it is a visua lization artifact caused by the imaging system Thus there can be no doubt as to the true shape of the moving structure Clearly the capabili ty of distinguishing between artifact and true structure outline plus the ability to create an image with a high line density makes the interlaced scanning method a very attractive display technique for use in an imaging system designed for the study of cardiac pathology

5 0 ECHOCARDIOGRAPHIC IMAGE RECORDING TECHNIQUES

The need to simultaneously display and record the echocardiographic image immediately leads the designer of a real time ultrasonic imaging system to an analysis of the available means of performing this function A strong desire to provide a system which allows instant playback of the recorded images focuses the attention of the designer onto the various ways one can use video tape recorders to provide the recording capability Fig 6 illustrates a tech nique in which a video tape recorder in conjunction with a television moni tor may be used The ultrasonic image is first formed on the cathode ray tube screen of the "X Y Monitor This device is under the direct control of the signals which represent the instantaneous position of the ultrasonic beam in both the horizontal (X) and vertical (Y) directions and the signal which represents the amplitude and duration characteristics of the returning echo ("Z) In front of this monitor is placed a television camera which utilizes a vidicon photoconductive camera tube A vidicon converts the optical ult rasonic image appearing on the X Y Monitor screen into a television image by the use of an electron beam scanning a photoconductive target placed in the focal plane of the camera s lens The resultant electronic signals from the television camera which represent the original ultrasonic image can now be displayed on a television monitor or recorded by a video tape recorder Since the format in which the television image is scanned onto the televi sion monitor s cathode-ray tube screen is entirely different than the

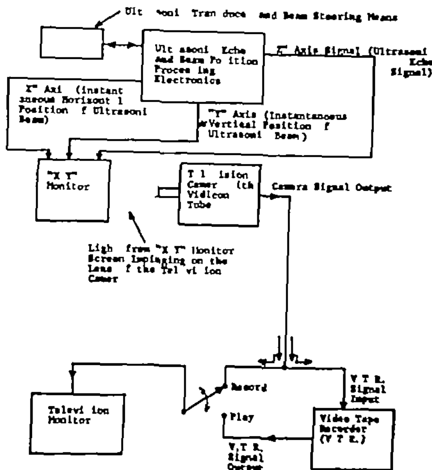


Fig 6 Vidicon scan converter system for simultaneously displaying and recording an ultrasonic image

scanning format as sociated with the ultrasonic image this process is called scan conversion

Vidicon scan conversion has the benefit of being very simple to implement with devices that are inexpensive and readily available It however has some significant drawbacks due to the nature of the vidicon tube itself and the characteristics the system must possess to be able to perform the scan conversion function In order to properly act as a scan convertor the vidicon s photoconductive target must have the ability to retain the electrical impression of the image being viewed the ultrasonic image for the time required to scan this image on the X Y Monitor s screen plus the time required to scan one television field Fig 7 shows this graphically Panel A shows the relative position between the television scan line and the ultrasonic data line at the start of the scan conversion process At the instant in time illustrated the television scan line has traversed the entire horizontal width of the vidicon s target while the ultrasonic data line has traveled from its origin the apex of a triangular shaped sector in this example to the equivalent of approximately 4 centrimeters of body tissue It can be seen from the schematic representation that the T V scan line intersects the ultrasonic line of data in only one place This occurs because of the radically different scan rates and scan directions associated with the two display systems Panel B depicts the situation that exists approximately a millisecond after the scan conversion has been initiated Lines that have already been scanned appear as dashed lines The resulting television image will be composed of the intersections between the tele

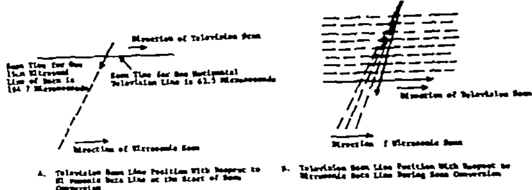


Fig 7: The operation of a vidicon scan convertor

vision scan lines and the scan line which comprise the optical ultrasonic image If there was no mechanism to maintain the electrical impression of the optical image on the vidicon s photoconductive target the intersection of the television scan lines and the ultrasonic image scan lines would seldom occur because by the time the television scan lines reach the bottom of the photoconductive target (this requires 16 7 milliseconds in the N T S C television system used in the United States) the scan lines associated with the earlier portions of the optical ultrasonic image would no longer be available Thus no television image would be formed There are two ways to overcome this difficulty The first way would be to use an X Y monitor that utilizes a cathode-ray tube with a long persistance phosphor This would have the effect of retaining the optical image on the monitor screen for a long enough period of time to assure that proper scan conversion occurs The second method would be to use a vidicon tube which employ a photoconductive target with the appropriate image retention characteristics

It must be noted that the persistance associated with the scan conversion process will alter the final appearance of the echocardiographic image displayed on the television monitor This is due to the fact that once the optical image is scanned by the television scanning system no mechanism exists to immediately erase this temporarily stored image Instead the image fades away over a period of time determined by vidicon and cathode ray tube characteristics Thus the following ultrasonic field or frame will overwrite on top of the earlier image (In actuality it may require three to five television frames for the first ultrasonic image to fade to the point at which it can no longer be seen) Each individual television image therefore contains history" from previous ultrasonic events

When the television image is *recorded* *either* by a photographic method or by the use of a video tape recorder the history artifact is also recorded The

resulting image therefore presents cardiac structures which are ill defi ned due to position uncertainties In addition to this aberation the non uniform manner in which past cardiac images fade causes single field tele vision images like those obtained when the image from a video tape recor- der is frozen by stopping the forward motion of the video tape to appear unevenly illuminated Clearly the longer the vidicon scan convertor s per- sistance characteristic the worse the history artifact and the better the uniformity of illumination associated with the final stopped two dimensional cardiac image

Another means for simultaneously displaying and recording the echocardiogra phic image is shown in fig 8 The system illustrated is referred to as the direct ultrasonic recording and display method This name is appropriate because the electronic signals associated with the echocardiographic image are displayed and recorded without use of a scan convertor Therefore the image visualized is always a direct reproduction of the original cardiac imaging signals As is the case for the vidicon scan conversion technique the echocardiographic image is first displayed on the screen of an X Y moni tor However in this system much care is taken to assure that the X Y image format can be time synchronized with a television image format This means that the ultrasonic imaging system is designed such that each ultra sonic field is scanned in 16 7 milliseconds Thus by the use of the appro- priate electronic configuration the ultrasonic imaging system can be syn chronized with a standard video tape recorder thereby allowing the origi nal ultrasonic signals to be recorded onto video tape Under these circum- stances the X-Y monitor serves only as a means to view the echocardiographic image before and after recording

There are two significant benefits associated with the direct ultrasonic display and recording approach The first is that the recorded and displayed echocardiographic images are free of artifacts produced by necessary system persistance On the surface this statement seems to require no further expla nation In fact however it has some non obvious implications Since the displayed and recorded images are always composed of original ultrasonic data the amount of history artifact is only a function of the type of phosphor used in the cathode ray tube of the X Y monitor used to display the image In addition if a frozen image is displayed by stopping the forward mo tion of a video tape that had been previously recorded the image being vie- wed will be totally free of history artifact and be evenly illuminated over the entire area of the image This is true regardless of the type of

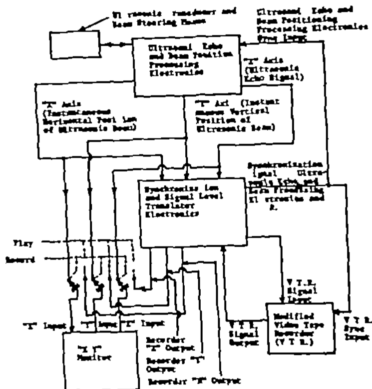


Fig 8: Direct ultrasonic recording and display system.

phosphor used in the X Y monitor The reason for this stems from the fact that a video tape recorder utilizes a rotating record-playback head that will play back a complete single field of ultrasonic information when the forward tape motion is halted Since there is no history artifact or fading associated with the original ultrasonic data and these aberations are caused either by previous ultrasonic fields being overwritten onto the field currently being displayed or the ultrasonic field fading before complete scan conversion takes place the frozen single field image being shown will be free of these artifacts

The second benefit is the ability to record a full 15 centimeter tissue depth ultrasonic image and play back this image with any desired tissue depth up to 15 centimeters This capability is derived from the fact that the original ultrasonic image signals are available at the time the recorded echocardiographic images are played back thus allowing a change in the tissue depth displayed by simply changing the electronic sweep rate associated with the depth-dimension of the X Y monitor Since a system which utilizes a scan conversion process does not allow the retrieval of the original ultrasonic data it cannot readily provide this feature

6 0 CONCLUSIONS

It was the purpose of this discussion to analyze the principles of two-dimensional real time echocardiographic imaging and from this analysis develop the system ideally suited for the performance of this function In general it has been shown that a mechanical sector scanner which ultrasonically scans the surface of the chest in 16 7 milliseconds in conjunction with a direct ultrasonic display and recording system, presently represents the real time cardiac imaging device that comes closest to fulfilling all of the clinical requirements This conclusion is based on the fact that the combination of elements described above utilizes the smallest echocardiographic window provides the least amount of image distortions and ambiguities and provides clear uniformly illuminated two-dimensional stop motion images which do not display a "history artifact

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THE CROSS-SECTIONAL ECHOCARDIOGRAM IN CLINICAL CARDIOLOGY APPLICATIONS AND RELATIONSHIP TO THE M-MODE TECHNIQUE

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SUMMARY

Until recently M-mode echocardiography has been the standard in clinical practice Although the M-mode systems provide rapidly acquired high resolution data concerning regional cardiac interface position and motion the limited area encompassed by the narrow M-mode beam and failure to provide spatial orientation may be a significant limitation in selected clinical areas

Cross-sectional echocardiography expands the area of the heart which is available for study and displays the acoustic images in a dynamic spatially oriented format allowing the moving cross-sectional anatomy of the heart to be visualized This variation in method of display provides more extensive information concerning valvular heart disease by permitting analysis of the morphology and motion patterns of the cardiac valves direct visualization of valvular orifices and appreciation of valvular movement in relationship to surrounding cardiac chambers In patients with ischemic heart disease the cross-sectional systems increase the area of the ventricle which is available for ultrasonic study by adding the cardiac apex and the medial and lateral walls of the ventricle to the recorded data In addition the systems permit localized distortion in left ventricular shape and function to be evaluated Finally in congenital heart disease the cross-sectional systems permit the orientation of the great vessels and cardiac chambers to be determined In this report we have presented examples of the applications of cross sectional echocardiography in each of these areas in the hope that the reader can gain from these isolated examples an overall appreciation of the potential of this type of instrumentation and its relationship to be more conventional M-mode display

6 0 CONCLUSIONS

It was the purpose of this discussion to analyze the principles of two *dimensional real time echocardiographic* imaging and from this analysis develop the system ideally suited for the performance of this function In general it has been shown that a mechanical sector scanner which ultrasonically scans the *surface of the chest in 16 7 milliseconds* in conjunction with a direct ultrasonic display and recording system presently represents the real time cardiac imaging device that comes closest to fulfilling all of the clinical requirements This conclusion *is based on the fact* that the combination of elements described above utilizes the smallest echocardiographic window provides the least amount of image distortions and ambiguities and provides clear uniformly illuminated two-dimensional stop motion images which do not display a history artifact

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Although the cross-sectional systems have only recently become available for clinical trial preliminary data already suggests that the enlarged field of vision and spatial orientation they provide will markedly enhance the diagnostic potential of cardiac ultrasound In this discussion specific applications of cross sectional echocardiography in valvular ischemic and congenital heart disease will be described It is hoped by these individual examples to illustrate both the general types of information these systems can provide as well as the relationship of cross sectional and M-mode echocardiography

1 VALVULAR HEART DISEASE

a Visualization av A-V Valve Morphology Mitral Valve Orifice Size

The observation by Edler that the motion pattern of the echo from the anterior mitral leaflet differed in patients with mitral stenosis when compared to normals represents the initial clinical application of echocardiography (8-9) Since this observation the diagnosis of mitral stenosis has remained the keystone of clinical echocardiography Although there have been refinements in the M-mode diagnosis of mitral stenosis the original methods for quantitation of severity based on the relative decrease in the initial dias tolic closing or E F slope remain unchanged Fig 1 is a typical M-mode recording from a patient with mitral stenosis illustrating the characteristic changes in leaflet motion including the reduced diastolic or E F slope Although the E F slope clearly reflects the distending pressure or pressure gradient to which the anterior leaflet is subject during diastole it is also affected by factors other than mitral valve orifice size such as a) the severity of fibrosis or calcification of the leaflet b) the compliance of the ventricle c) the rate of flow through the mitral valve orifice and d) the diastolic motion of the posterior ventricular wall to which the leaflet is attached Not surprizingly therefore it has recently been shown that at tempts to assess the severity of the stenotic lesion using this slope may be misleading in individual cases (10)

The ideal method for evaluating mitral stenosis would be to directly visuali ze the stenotic mitral valve orifice which is the critical determinant of severity In 1974 Henry et al using a prototype mechanical sector scanner demonstrated that direct visualization of the mitral valve orifice was indeed possible with the cross sectional technique (11) These authors observed an excellent correlation between the mitral valve orifice size measured from the cross sectional echogram and the directly measured mitral valve orifice

INTRODUCTION

The use of pulsed reflected ultrasound as a means of visualizing intracardiac structures is now well established (1 2) Untilrecently the M-mode echocardiogram has been the standard in clinical practice (3) The M-mode display permits recording of both the depth and motion patterns of intracardiac reflective interfaces relative to a fixed spatial reference and time The high resolution and rapid sampling rate of the M-mode system makes it an ideal method for studying an organ whose component parts display rapid and complex motion such as the heart The M-mode echocardiogram is limited however in that it only provides information concerning the relative position and motion of structures along the narrow path of the ultrasonic beam Thus with the transducer held stationary a very limited area of the heart is visualized at any given time In many areas of cardiac diagnosis such as congenital and ischemic disease the spatial or lateral relationships of cardiac structures or areas of segmental dysfunction may be more important than distance and motion pattern along the beam axis

The initial attempts to add spatial orientation to the M-mode echogram led to the development of M-mode scanning techniques (4) Using an M-mode scan it is possible by sweeping the transducer from one area of the heart to another while continuously recording to derive some information concerning the spatial relationships of the structures examined Unfortunately these scans vary with the speed and path of transducer movement and hence are qualitative at best In addition since both direction and speed of transducer angulation will vary from sweep to sweep and from examination to examination the reproducibility of these data is limited

The continued need for more quantative spatial information concerning cardiac structure and function led to the development of the two-dimensional or cross sectional echocardiographic systems (5 7) With these systems the beam of ultrasound is either mechanically or electronically swept through a predetermined path while the relative position of the beam in space is continuously recorded In this manner the individual lines of acoustic data can be displayed in an appropriate spatial relationship to one another and as a result the cardiac structures which they reflect visualized in a correct spatially oriented format In addition by rapidly sweeping the beam of ultrasound across the field of examination (i e faster than the flicker vision of the eye) dynamic motion can be added to the cross sectional display While the cross sectional techniques does not provide new acoustic data the method of display permits information to be appreciated and utilized which was here-to-fore meaningless in the absence of a spatial reference

correlation (r 0 95) between the echocardiographic measurement of mitral valve orifice size and the hemodynamic estimate of mitral valve area (12) In a group of 40 patients examined in this laboratory with both isolated stenosis and stenosis with insufficiency a similar correlation was obtained (r = 0 90) (13) Fig 2 is a cross-sectional echogram corresponding to the M-mode recording in fig 1 In the left hand panel the mitral valve orifice is directly imaged during diastole The measured valve area of 1 3 cm^2 compared with a valve area of 1 2 cm^2 determined at cardiac catheterization

These data collected from three separate centers using independently developed imaging systems suggests that cross sectional echocardiography is a valid non-invasive method for direct visualization of mitral valve orifice size is applicable in approximately 90% of patients and correlates with pathologic and hemodynamic determination of mitral valve area

B Semilunar Valve Morphology and Motion Patterns

The evaluation of semilunar valve motion and detection of stenosis is another area where cross-sectional echocardiography has been of particular value While direct visualization of the valve orifices has proven difficult examination of the long axis morphology and motion patterns of these valves has permitted detection of stenosis appreciation of leaflet separation and in some cases estimation of severity (14 15) In this section we will examine the relative merits of the M-mode and cross sectional system in examining patients with valvular pulmonary stenosis Patterns of aortic valve motion are similar and will be discussed later in this symposium in the section on left ventricular outflow obstruction

The M-mode diagnosis of valvular pulmonary stenosis rests on the observed effects of altered right ventricular and pulmonary artery pressure relationships on pulmonary leaflet motion (16) Patients with valvular pulmonary stenosis frequently have a decrease in right ventricular compliance and increased force of right atrial contraction which in the face of normal or low pulmonary artery pressure results in a positive pressure gradient across the valve at end diastole This pressure gradient produces an opening or doming motion of the valve leaflets following atrial contraction which is reflected by an increase in the normal posterior deflection of the posterior pulmonary leaflet following atrial contraction (A wave depth) (fig 3)

Unfortunately the diagnostic value of these observations is limited by 1) technical difficulty in recording the pulmonary valve 2) the indirect nature of the derived data 3) lack of specificity of the hemodynamic abnormality

area at surgery or from pathologic specimens In 13 of their 14 patients the echocardiographic orifice size was within 0 3 cm^2 of the directly mea sured mitral valve area In a subsequent study Nichol et al were able to record the mitral valve orifice in 25 of 30 patients undergoing cardiac catheterization for isolated mitral stenosis and observed an equally excellent

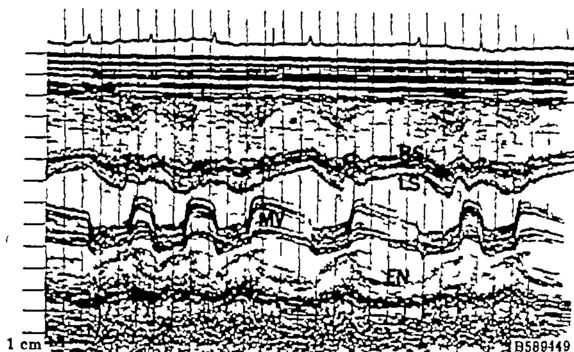


Fig 1 M-mode echocardiogram from the patient with mitral stenosis demonstrating the typical echocardiographic features of the stenotic mitral valve There is an increase in echo production from the diseased anterior and posterior leaflets decrease in opening amplitude of the anterior leaflet anterior motion of the posterior leaflet during diastole and a decrease in the diastolic or E to F slope RS = right side of the interventricular septum LS = left side of the interventricular septum MV = mitral valve EN = posterior wall endocardium



Fig 2 Short axis cross-sectional scan recorded with the plane of the cross-sectional scan oriented parallel to or directly across the mitral valve orifice The left hand panel is recorded during diastole and illustrates the thickened fibrotic mitral commissures with a decrease in effective mitral valve orifice area MVO = mitral valve orifice The right hand panel recorded during systole illustrates the closed systolic configuration of the mitral valve (MV) The echocardiographic mitral valve orifice in this case measured 1 3 cm^2 compared to a mitral valve area calculated at cardiac catheterisation of 1 2 cm^2

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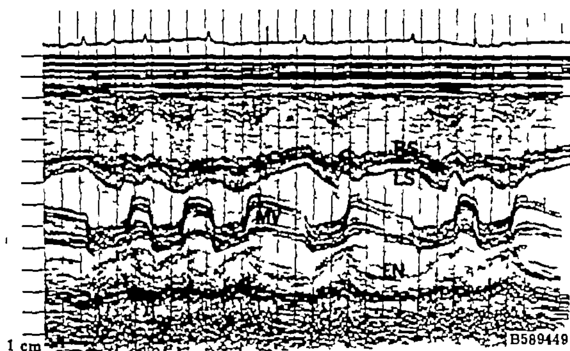


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and 4) the general failure of these changes to occur in patients with mild stenosis (17)

The cross sectional technique simplifies the diagnosis of valvular pulmonary stenosis in several ways (18) First the enlarged field of vision provided by this technique facilitates location and recording of the pulmonary artery and valve Secondly the ability to view the entire domed stenotic valve during systole permits direct determination of stenosis in patients with mild as well as severe obstruction Fig 4 is a cross-sectional recording of a normal pulmonary valve illustrating the normal systolic position of the fully opened pul monary leaflets lying parallel and in close proximity to the anterior and pos terior margins of the pulmonary artery In contrast fig 5 is a recording from a patient with moderately severe valvular pulmonary stenosis In this case the pulmonary leaflets arc inward toward the center of the lumen of the pulmonary artery markedly reducing the separation between the leaflet echoes at the valve orifice In a series of 22 patients with valvular pulmonary stenosis examined in this laboratory we were successful in recording the pulmonary valve in 20 cases (18) In each case in which the valve was recorded the characteristic systolic doming of the leaflets was evident In each of 7 pa tients with mild pulmonary stenosis and normal A waves on the M-mode record systolic doming of the valve was observed on the cross sectional recording These observations suggest that the cross sectional technique should offer a more sensitive and specific method for evaluating the presence of pulmonary valve morphology and detecting valvular pulmonary stenosis

C Motion of Cardiac Valves in Relation to Surrounding Structures Mitral Valve Prolapse

In addition to direct visualization of the diastolic mitral valve orifice and the systolic configuration of the stenotic semilunar valves the cross-sectional systems also permit examination of the motion patterns of the cardiac valves in relation to their supporting structures and contiguous cardiac chambers This is particularly important when attempting to diagnose the mitral valve prolapse syndrome

The inital observations by Dillon et al (10) and Kerber et al (20) of prominent mid systolic posterior displacement of the mitral leaflets during sys tole in patients with mitral valve prolapse suggested that M-mode echocardiography might offer a simple reliable non-invasive method for objectively defining the presence of this abnormality Following these observations however difficulties in appropriately recording the abnormal leaflet motion and defi ning objective criteria for the diagnosis of prolapse have arisen (21 22)



Fig 3 M-mode echocardiogram of the pulmonary valve from a patient moderately severe valvular pulmonary stenosis Opening of the pulmonary valve is initiated following the P wave of the electrocardiogram (P) at which time there is a marked posterior or opening deflection of the pulmonary leaflet (A wave) Following this deep A wave the leaflet returns to a base line or closed position prior to the onset of ventricular systole (E) The very large A waves seen in this case reflect presystolic opening or doming of the valve The [illegible]se of the A waves with their presence du[ring] both phases of the respiratory cycle are consistent with moderate to severe disease (From Weyman A E Pulmonary Valve Echo Motion in Clinical Practice Amer J Med 62 843 1977)

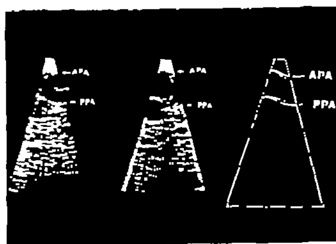


Fig 4 Cross-sectional echogram recorded with the scan plane oriented parallel to the long axis of the pulmonary artery in a normal patient The left hand panel (Panel A) is recorded during diastole and illustrates the coapted pulmonary leaflets lying in the center of the pulmonary artery (horizontal arrow) The middle panel (Panel B) is recorded during systole In this panel the pulmonary leaflet lie in a fully open position parallel to the margins of the anterior and posterior surfaces of the pulmonary artery (vertical arrows) The right hand panel (Panel C) is a line drawing corresponding to Panel B

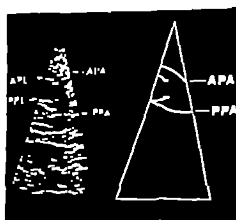


Fig 5 Cross-sectional recording from a patient with valvular pulmonary stenosis demonstrating the characteristic configuration of the stenotic pulmonary valve The anterior and posterior pulmonary leaflets of the domed valve curve into the lumen of the pulmonary artery reducing the valve orifice and producing restriction to right ventricular outflow



Fig 6 M-mode echocardiographic scan of the left ventricle from the area of the aortic root and left atrium (on the left) through the mitral valve to the cardiac apex (right hand portion of the scan) This scan illustrates the normal contraction sequence of the left ventricle as well as providing a general concept of the shape of the left ventricular chamber

state remains to be defined Further preliminary data suggest that the expression of complications of mitral prolapse such as the presence of ectopic beats and ventricular tachycardia does not correlate with the severity of the anatomic derangement Despite these difficulties the cross sectional echogram should represent an ideal method for visualizing the mitral valve leaflets in patients with mitral valve prolapse syndrome and hence increase our knowledge in this area

II ISCHEMIC HEART DISEASE

A. Left Ventricular Structure and Function

Probably nowhere else are the strengths and the weaknesses of the M-mode techniques as apparent as in the study of the left ventricle (25) Fig 6 is a typical M-mode scan of the left ventricle beginning at the aorta and left atrium and continuing through the cavity of the ventricle into the region of the cardiac apex The high resolution of the M-mode system clearly displays the endocardial and epicardial surfaces permitting determination of left ventricular wall thickness and thickening with systolic contraction while the rapid sampling rate permits detailed definition of the motion patterns of these interfaces relative to time In addition the scanning technique conveys an impression of overall left ventricular shape Combining these features provides valuable information

Since mitral valve prolapse may be associated with a number of major compli cations such as sudden death intractable congestive heart failure recurrent ventricular tachyarrhythmias and bacterial endocarditis it is highly important if possible to clearly define the patient group with this disorder

Studies to date using the cross-sectional technique have already helped to clarify many of the problems which have arisen during M-mode study It was initially recognized by Sahn et al (23) that the prolapsing mitral leaflets move superiorly away from the left ventricle into the cavity of the left atrium rather than posteriorly as suggested by the M-mode record The path of motion of the prolapsing leaflets is therefore perpendicular to the M-mode beam in many cases causing leaflet motion to be poorly recorded In addition the normal motion of the left ventricle during systole is anterior and inferior while the motion of the prolapsing leaflets is in the opposite superior and posterior direction If the magnitude of these vectors is comparable then the spatial motion of prolapsing leaflets may be neglible and hence poorly appreciated Finally when visualizing the mitral leaflets with the M-mode echocardiogram one can only detect motion relative to a fixed reference point If the transducer is placed superior to the mitral valve therefore the normal inferior motion of the mitral ring during ventricular systole will result in the mitral leaflets moving away from the transducer or posteriorly on the M-mode record This may lead to an inappropriate diagnosis of mitral valve prolapse

The cross sectional technique in contrast permits the leaflets to be visualized throughout the cardiac cycle in their proper spatial position With this type of visualization it is possible to see both systolic and diastolic motion of the leaflets in relation to the entire mitral valve apparatus and to relate the amplitude of superior motion of the mitral leaflets to the remainder of the left ventricle and left atrial cavity (24) It is also possible to record leaflet motion during periods of induced physiologic stress such as increase in afterload change in patient position maneuvers to decrease left ventricular volume and administration of pharmacological agents all of which change the relative size of the left ventricular cavity and affect the degree of prolaps Studies to date using the cross sectional systems have demonstrated a clear difference in the motion pattern of the mitral valve in patients with classic mitral valve prolapse when compared to normals (24) It appears unfortunately that there is a wide spectrum of mitral leaflet motion varying from very minimal backward or superior motion of the leaflets during systole to unequivocal prolapse The point at which motion of the mitral leaflet toward the left atrium ceases to be a normal variant and represents a pathologic



Fig 7: Cross-sectional echocardiogram of the cardiac apex The apical endocardium (EN) as well as the epicardial (EP) surface in the region of the cardiac apex can be visualized The line drawing to the right of the figure illustrates the normal contraction sequence of the apex

of regional dysfunction to be appreciated These topics will be discussed in greater detail in the section on the evaluation of the ischemic ventricle by cross sectional echocardiography later in this symposium.

III CONGENITAL HEART DISEASE VENTRICULAR SITUS AND GREAT VESSEL ORIENTATION

In the evaluation of congenital heart disease determination of the location and relative position of the great vessels and cardiac chambers is of paramount importance Abnormalities of great vessel orientation or transposition of the great vessels represents the commonest form of cyanotic congenital heart disease in newborns (26) Prior M-mode observations suggested that the diagnosis of d transposition could be inferred by recording two parallel great vessels one on top of the other with simultaneous recording of the semilunar valves (fig 8) (27) As previously noted in other sections however attempts to establish spatial relationships from the limited area of the heart visualized by the M-mode technique may be misleading Thus it was subsequently noted that in young children especially if the transducer was placed higher than usual on the chest the close proximity of the AV valves made it possible to record these structures simultaneously giving an appearance similar to that seen with transposition (28) In addition if the heart is shifted rightward due to a malformation of the lungs or thoracic cage a similar picture can be obtained Thus while in the majority of cases the M-mode technique is a useful means for detecting the presence of transposition in individual instances these data may be misleading

In a recent report Henry et al described a method for differentiating anomalies of the great vessels using the cross sectional system (29) Their observations based on necropsy studies indicate that three basic relationships exist between the great arteries as they exit the heart Normally the two great vessels cross at their origin with the right ventricular outflow tract and pulmonary artery passing diagonally above the aorta In contrast with transposition complexes the two great vessels leave the heart parallel to one another

concerning cardiac structure and function in the areas examined Further the format in which the M-mode display is recorded is very convenient for data acquisition and analysis

As previously noted however the limited area of the left ventricle transsected by the M-mode beam represents a significant limitation in assessing left ventricular structure and function in the segmentally diseased ventricle In this regard a consideration of the data not presented in fig 6 is important First as the scan approaches the cardiac apex the echoes from the anterior and posterior endocardial surfaces abruptly cease This is characteristic of these scans and occurs because the apex lies relatively parallel to the path of the ultrasonic beam and therefore is not an appropriate reflector making M-mode recording of this area difficult In addition the scan visualizes only a single slice of the beam through the ventricle The remaining semicircular medial and lateral walls which comprise the majority of the left ventricular muscle mass are not included Thus the non visualized area of the ventricle is larger than that which is recorded and in patients with segmental disease may be of greater diagnostic significance

Cross sectional echocardiography is an important adjunct in the evaluation of the left ventricle in a number of areas First the spatially oriented display permits the medial and lateral walls of the left ventricle as well as the cardiac apex to be included in the echocardiographic images Secondly it allows lateral and oblique as well as axial motion to be recorded Lateral motion across the beam could not be quantitated with the M-mode technique and was merely reflected as presence or absence of echo production With the cross sectional display as a wall or structure moves across the plane of the scan its echoes will cross one spatially oriented line of acoustic data after another allowing its lateral motion to be tracked and recorded One can therefore record lateral motion by following the moving echo from line to line across the scan axial motion by movement of the echo relative to the transducer and oblique motion by a combination of the two Fig 7 is a recording of a long axis of the cardiac apex using the cross sectional system In this figure the motion pattern of the cardiac apex from left to right across the plane of the scan the inward contraction of the anterior and posterior walls and thickening of the ventricular myocardium during systole are evident By rotating the transducer 90^0 to record a short axis of the ventricle similar information concerning the medial and lateral walls can be obtained Thus by permitting visualization of the spatial geometry and motion pattern of the left ventricle the cross sectional system increases the area of the ventricle which can be examined and permits distortion in left ventricular shape as well as the location and extent

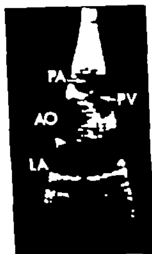


Fig 9 Short axis cross-sectional scan of the pulmonary artery and aorta The lateral half of the relatively circular aorta is visualised to the right while the half moon or sausage shaped pulmonary artery is recorded superior and to the left of the aorta (right hand side of the scan) Because the cross-sectional beam is oriented parallel to the short axis of the aorta this vessel has a normal circular configuration In contrast the plane of the scan is oblique to the pulmonary artery causing it to have a half moon or sausage appearance (From Feigenbaum H Echocardiography second edition Lea & Febiger Philadelphia 1976)

the contrasting pattern presented by the vessels when they exit the heart in a parallel fashion In this configuration the scan which is parallel to the short axis of one vessel will also be parallel to the short axis of the other Thus the two vessels will both appear circular In this example the aorta is superior to the pulmonary artery and both vessels have the expected circular appearance This type of image is analogous to looking down the barrel of a double barrelled shot gun

In patients with truncus arteriosus there is only one large vessel which appears as a single circle on the cross-sectional scan These concepts suggest a relatively simple and straight forward method for differentiating anomalies of position and relative orientation of the great vessels

The second problem which arises is the determination of ventricular situs Sahn et al noted that the configuration and motion pattern of the tricuspid valve is distinctly different than that of the two leaflet mitral valve (30)



Fig 10: Short axis cross-sectional echogram of the aorta and pulmonary artery from a patient with d-transposition of the great vessels In this recording both the larger superior aorta and the smaller inferior pulmonary artery appear circular This occurs because the great vess ls are aligned parallel to each other and therefore when the plane of the scan is oriented parallel to the short axis f one vessel it must be parallel to the short axis f the other resulting in a similar appearance of both vessels (From Feigenbaum, H Echocardiography second edition Lea & Febiger Philadelphia 1976)



Fig 8 M-mode echocardiogram from a patient with d-transposition of the great vessels The ultrasonic beam is scanned from the aorta and pulmonary artery on the left through the region of the mitral valve and into the left ventricle on the right The aorta (AO) and pulmonary artery (PA) run parallel to each other with no evidence of an intervening crista supraventricularis In addition echoes from both semi lunar valves are recorded simultaneously The echoes from the interventricular septum (IVS) are continuous with those from the anterior wall of the pulmonary artery The echoes from the mitral valve are continuous with the posterior wall of the pulmonary artery This recording is typical of the M-mode features of transposition of the great vessels (From Dillon et al Echocardiographic Manifestations of d-transposition of the Great Vessels Amer J Cardiol 32 74 1973)

Finally in patients with truncus arteriosus there is only a single large vessel Using the cross-sectional system they then demonstrated that when the great vessels cross at their origin the plane of the cross sectional scan can be aligned parallel to the short axis of only one of the two arteries As a result if the cross sectional scan is aligned parallel to the short axis of the aorta it must bydefinition be oblique to the short axis of the pulmonary artery When presented in this fashion the aorta appears as a relatively circular structure while the pulmonary artery assumes a halv moon or sausage shape Fig 9 is an example of the normal short axis appearance of the great vessels at the level of the aortic and pulmonary valves In this recording the aorta has a circular appearance while the pulmonary artery to which the scan is oblique appears to have a half moon or kidney shape Fig 10 is a recording from a patient with transposition of the great vessels illustrating

ACKNOWLEDGEMENT

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Since the tricuspid valve is normally associated with the anatomic right ventricle determination of the pattern of valvular motion permits an appreciation of the related ventricle and hence ventricular situs These observations concerning great vessel and cardiac chamber orientation when combined with prior cross sectional observations concerning levels and types of left and right ventricular outflow obstruction suggest that the cross sectional echogram will become a valuable non-invasive tool for the diagnosis and assessment for various forms of complex congenital heart disease

DISCUSSION

In this report we have highlighted a number of the clinical areas in which cross sectional echocardiography has already proven to be of diagnostic value These examples indicate that the increased field of vision provided by the cross sectional technique facilitates recording of individual cardiac structures and expands the area of the area of the heart which is available for echocardiographic study while the dynamic spatially oriented display permits a unique appreciation of cross sectional cardiac anatomy and function This combination of features expands enormously our ability to derive useful clinical data from the heart using pulsed reflected ultrasound

Although at first glance one might feel that the quality of the information obtained from the cross sectional images is so far superior to that obtained by conventional M-mode recording that the M-mode technique will rapidly be replaced While there are clearly clinical areas in which the cross sectional technique should surpass M-mode recording the high resolution rapid sampling rate and ease of data handling provide by the M-mode systems suggests that they will always find a place in the clinical examination It is envisioned that in the future one will utilize the cross sectional system to obtain an overall view of cardiac structure and function When detailed analysis of regional wall or valvular motion is required an M-mode recording of a selected portion of the scan will be obtained The cross sectional scan therefore will permit a more intelligent selection of the specific regions to be examined while the M-mode recording will provide precise information in a readily useable format concerning the particular area selected These combined features should provide the clinician with extremely useful and powerful tools for evaluating cardiac structure and function non invasively

IMPROVEMENT OF LATERAL RESOLUTION IN ULTRASONIC SYSTEMS

N BOM C T LANCÉE AND C M LIGTVOET

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INTRODUCTION

Resolution is the capability of echocardiographic systems to present separately closely lying structures The resolution is usually defined in two directions perpendicular to the sound beam (lateral resolution) and in the direction of the sound beam axis (axial resolution) If short ultrasonic pulses are used the axial resolution is in the order of one mm For present medical practice this seems acceptable In contrast the lateral resolution may constitute a major problem due to the finite beam width of ultrasonic devices As a result echoes which originate from off axis structures may be displayed as if they were originating from structures on the beam axis Both in time-motion (M-mode) registrations and two-dimensional imaging this distortion appears Only the way of presentation is different In an M-mode sectorscan the various cardiac structures are displayed as function of time and in a relation on the recording paper which is a function of the transducer aiming motion In a two-dimensional image the correct geometrical structure orientation is presented Thus if the beam shape in any two-dimensional imaging system and in single element M-mode registration were equal (which may be so with for instance a mechanical sectorscan) the errors which are introduced are the same

A broad beam width will cause many spurious echoes (1) The beam width is a function of depth and depends on the transducer geometry and frequency The most commonly used transducer in diagnostic techniques has the form of a disk which is arranged to transmit and receive energy at its surface The sound beam is usually described as the near field and far field zone For a given radius of the transducer the length of the near field zone increases with increasing frequency In this near field zone the energy is mainly confined in a cylinder with a radius corresponding to the radius of the transducer disk (2) In the far field or Fraunhover zone the energy is confined in a diverging central lobe and a number of secondary or side lobes The energy in the side lobes is usually much smaller than in the main lobe It should be realised that the beam pattern and the observed structures are three-dimensional thus interpretation of errors within one plane seems an oversimplification of the situation It should also be mentioned that the net

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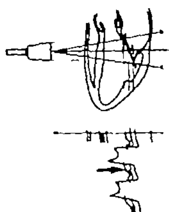


Fig 1 Sagittal cardiac cross-section with transducer and beam directions b and c from which erroneous echos may occur (see arrow)

In fig 2 a clinical example of this phenomenon is shown As is found in simular situations in reality the mitral valve was normal although the multiple mitral valve echoes during systole could suggest mitral valve disease Simularly echoes from the root of the aorta may sometimes contaminate the mitral valve registration and spurious ehoes are very apparent when highly reflecting structures such as prosthetic valves are insonified

ERRORS IN TWO-DIMENSIONAL IMAGING SYSTEMS

In fig 3 spurious echoes are schematically indicated for a linear array system and for a mechanical or phased sectorscan In the multiscan or linear array situation in addition to the correctly presented point reflector P on

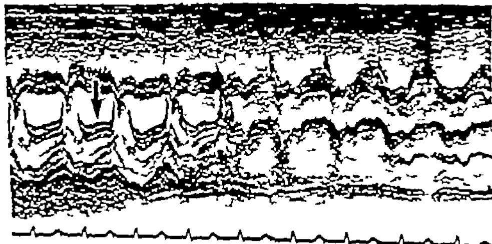


Fig 2: Clinical M-mode registration where multiple echoes are seen (arrow) possibly due to a situation as given in fig 1

effect of errors as they appear is also a function of parameters such as echo intensity gain settings transducer sensitivity and recording paper or display parameters

For a good lateral resolution a small beam width is required As a first step towards a better lateral resolution transducers were constructed with an acoustical lense This results in a fixed focal point Another method which is often followed is the introduction of a curved transmission and reception surface whereby the wave front will cause a focussing effekt at a fixed focal point The focussing characteristics depend on frequency and aperture size With constant aperture higher frequency results in better focussing Ultrasonic attenuation increases with frequency thus the upper selectable frequency is limited The transducer itself should remain relatively small for aiming purposes This limits the aperture size The main problem however is that with fixed focal point transducers only a better resolution in the vicinity of the focal point is obtained In diagnostic ultrasound the target is a continuous object and an optimal solution calls for focussing over the entire field of view This requires a dynamic focussing method

In the following an indication is given of the errors that occur in single element and two dimensional imaging systems due to limited lateral resolution Thereafter a solution will be described whereby a variable focussing is obtained electronically over the entire field of depth It will be indicated how this can be implemented in single element as well as in a multi-element linear array system

EXAMPLE OF M-MODE ERRORS

With an ideal pencil like ultrasonic beam the recorded echoes should represent the correct position of each reflecting structure on the beam axis In fig 1 this situation is schematically shown for that part of the reflecting anterior mitral valve leaflet through which the ideal beam passes in direction a Because of the imperfections in the beam width parts of the mitral valve in direction b and direction c are also creating an echo Since the transducer transmits a short pulse and all echo systems are based on travel time measurements only the reflections from point 1 near the aorta and point 3 near the tip of the mitral leaflet are erroneously represented as dots in brightness modulation as indicated in fig 1 The arrow indicates the double or triple echoes which are often seen in systole in the anterior mitral leaflet registration

The example shown at the top of Fig 4 shows no focussing at all with a flat wave front At the bottom point focussing is obtained if a curved wavefront is constructed for acoustic waves in reception by delay of the incoming signals This delay must be varied over the depth if a number of focus points are to result to cover the total depth Since the beam pattern and the resulting lateral resolution is a function of the configuration in transmission and in reception some gain may be obtained by insertion of an axicon focussing in transmission as also shown in Fig 4 The optimalisation of the array was performed with a computermodel Calculation showed that for an effective focussing of 16 cm scandepth and with a given fundamental transducer a frequency of 3 12 MHz and aperture of 24 mm is needed As an example a phased array transducer can be included in a linear array transducer and a so called linear phased array transducer is formed In this situation a number of small elements will be used together as a subset of the entire linear array Each focussing activity then will be repeated for an adjacent subset of elements The subarray is divided into 12 elements of 2 mm width each This results in a lateral spacing of 2 mm between two adjacent scans For each application and frequency an optimal configuration can be calculated For the linear array two-dimensional imaging transducer the principle was applied resulting in a new probe of 51 elements in total In the earlier twodimensional imaging system with the linear array principle we used 20 element-probes In Fig 5 the beam width defined as the lateral position where the sound intensity has dropped to 10 dB as function of the depth is shown for the original 20 element system and for the 51 element dynamic focus

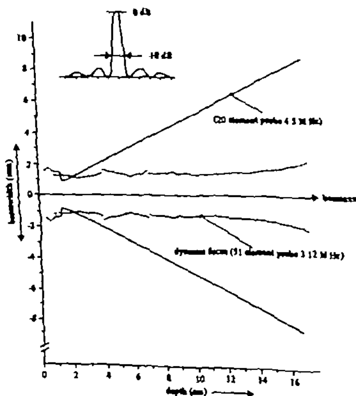


Fig 5: Lateral beam resolution as measured at - 10 dB as function of depth for the 20 element focussed linear array probe compared with the dynamically focussed 51 element probe



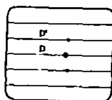
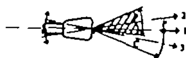
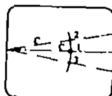
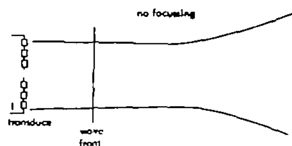


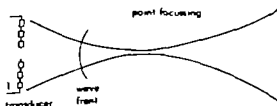
Fig 3 Image deformation diagrammatically constructed for a rectangularly and sectorially formed image (from Echocardiology N Bom editor published by Martinus Nijhoff the Hague 1977)

the display at distance D adjacent elements will see this reflector erroneously at distance D The situation has been indicated for an arbitrary beam opening angle α. On the display curved distorsion will appear A simular situation will occur with the sectorscan as shown at the bottom of fig 3 If the mechanically or electronically swept beam is pointing in direction 1 then reflector P is correctly represented on the display in beam direction 1 If however this beam is directed towards direction 2 then again P is seen and an echo presented on the display Thus a slight curventure will result at a depth C much simular but in opposite direction to the one just described for the linear array system







DYNAMIC FOCUSSING (3)

If a transducer consists of a number of small elements it becomes possible to vary the pulse travel time between each individual element of the transducer and the focal point by means of electronic delay methods With such a phased array transducer it is possible to maintain a good lateral resolution over the entire scan depth In fig 4 the principle is explained schematically in the situation of linear array transducer For each scan of the linear phased array a subset of elements is used as phased array

Fig 4 Illustration of focussing possibilities with subset of elements From top to bottom respectively no focussing axicon focussing as may be obtained in transmission and point focussing by introduction of a curved front in reception

to frame or combinations in transmission and reception might be used to achieve optimal resolution

In this paper a system for dynamically focussing over the entire depth and over the complete two-dimensional image was described with focussing in the array plane only Two prototypes are in operation and have been tested in various clinics The improvement showed to be a step forward again and will certainly carry the applications beyond todays use where only direct observations of gross changes in dynamics and geometry of the heart in motion are studied

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Fig 6 Transducer for high resolution M-mode registrations Transducer face (top) with individual circular symmetric elements The complete transducer is shown as well (bottom)

sing system The gain in lateral resolution is particularly in deeper areas substantial It may be concluded that with such parameters a reasonably good resolution can be maintained over the entire depth and thus over the entire 2 D image Detailed information was further published by Ligtvoet (see ref 3)

The above described method is also applicable to single element M-mode technique be it that for optimum lateral resolution here circular elements can be used This does result in improvement of resolution in all directions perpendicular to the beam axis as well as over the entire depth Again the optimum combination of the geometry number of rings and frequency must be calculated As an example a disk shaped transducer for M mode registrations is shown in Fig 6

DISCUSSION

With the introduction of the dynamic focus an entire new generation of equipment was introduced Not only is the transducer of e g the two-dimensional imaging system much more complex with its 51 elements also the electronic processing for transmission as well as reception is much more complicated Future will tell if in practice the inherent complexity and thus increased costs of such improvements are indeed necessary for routine use

It should be emphasized that here described focussing in two-dimensional images with a linear one dimensional array has been obtained as function of depth and in the plane of the array only Lateral resolution will be improved if in future also focussing in the plane perpendicular to the array plane is introduced Alais suggested for instance focussing with a two-dimensional array and phase and antiphase steering of the elements to obtain three-dimensional focussing (4) In future such focussing may also be carried out with array configurations and signal processing equal or simular to the one described here but with additional acoustic element surfaces active and positioned in a plane perpendicular to the described array plane Beam pattern variation from frame

to frame or combinations in transmission and reception might be used to achieve optimal resolution

In this paper a system for dynamically focussing over the entire depth and over the complete two-dimensional image was described with focussing in the array plane only Two prototypes are in operation and have been tested in various clinics The improvement showed to be a step forward again and will certainly carry the applications beyond todays use where only direct observations of gross changes in dynamics and geometry of the heart in motion are studied

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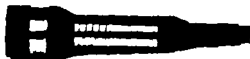


Fig 6 Transducer for high resolution M-mode registrations Transducer face (top) with individual circular symmetric elements The complete transducer is shown as well (bottom)

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DISCUSSION

With the introduction of the dynamic focus an entire new generation of equipment was introduced Not only is the transducer of e g the two dimensional imaging system much more complex with its 51 elements also the electronic processing for transmission as well as reception is much more complicated Future will tell if in practice the inherent complexity and thus increased costs of such improvements are indeed necessary for routine use

It should be emphasized that here described focussing in two dimensional images with a linear one dimensional array has been obtained as function of depth and in the plane of the array only Lateral resolution will be improved if in fu ture also focussing in the plane perpendicular to the array plane is introdu ced Alais suggested for instance focussing with a two-dimensional array and phase and antiphase steering of the elements to obtain three-dimensional focus sing (4) In future such focussing may also be carried out with array confi gurations and signal processing equal or simular to the one described here but with additional acoustic element surfaces active and positioned in a plane perpendicular to the described a ray plane Beam pattern variation from frame

to frame or combinations in transmission and reception might be used to achieve optimal resolution

In this paper a system for dynamically focussing over the entire depth and over the complete two-dimensional image was described with focussing in the array plane only Two prototypes are in operation and have been tested in various clinics The improvement showed to be a step forward again and will certainly carry the applications beyond todays use where only direct observations of gross changes in dynamics and geometry of the heart in motion are studied

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Fig 6 Transducer for high resolution M-mode registrations Transducer face (top) with individual circular symmetric elements The complete transducer is shown as well (bottom)



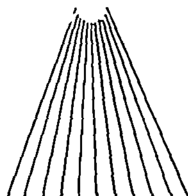
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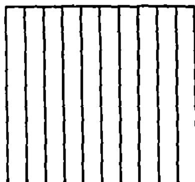
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Fig 2


Fig 3

In mechanical sector scanners there is a single element transducer not unlike that used in standard ultrasound instrumentation This single element transducer is moved rapidly through an arc which varies from 0 degrees to approximately 60 degrees The electrical sector array approach utilizes a phased linear array in which the ultrasound beam is electronically steered at angles ranging from 0 to 90 degrees This type of instrumentation is primarily used for cardiology applications in that the transducer s head size and resultant field of view is most suited for imaging thru the small intercostal spaces present in ultrasound cardiology examinations However the sector array type of instrumentation is not optimally suited for abdominal imaging because of its pie-shaped field of view There is also the disadvantage that with the sector array approach the area of the resultant beam having maximum line density directly corresponds to the area of minimum field of view Conversely the area having the maximum field of view is also the area of minimum resolution due to the change in lind spacing which increases as a function of depth (see fig 2)

The linear array system has a rectangular field of view and ranges in electronic complexity from totally unfocused to focused on both transmit and receive

Because of its rectangular field of view the linear array system is ideally suited for abdominal imaging However the physical size of the array makes it less effective in other applications The limitations of field of view and loss in resolution with increased depth is overcome due to the uniform field of view (see fig 3)

We have elected to go with the linear array system as it is ideally suited for abdominal imaging and has potential in other areas of application such as breast thyroid and cardiology

ULTRASOUND FLUOROSCOPY - WHAT IS IT AND OUR APPROACH TO YOUR REQUIREMENTS

J A MCLAIN

From the Unirad Corporation Subsidiary of Ohio-Nuclear A Technicare Company Denver Colorado USA

ABSTRACT

A discussion on Ultrasound Fluoroscopy and how it relates to the traditional Real Time Instrumentation

This paper covers the various types of Ultrasound Fluoroscopy Instrumentation a few of the advantages and disadvantages of each and Unirad Corporation's approach to Ultrasound Fluoroscopy Also detailed discussions on the technical differences between their approach and the traditional Real Time Instrumentation itemizing electronic beam resolution control in some detail as to its advantages complexity and comparison to Real Time (Non-focused) and the traditional single element Ultrasound Instruments

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Ultrasound Fluoroscopy is an imaging technique which in the past has also been referred to as real time imaging However even though Ultrasound Fluoroscopy and Real time imaging may appear to be the same there are major technical differences some of which will be covered in this paper The types of instrumentation available in Ultrasound Fluoroscopy fall into two separate categories

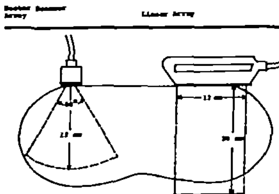


Fig 1 Field of view comparison. Abdominal scan

The differences in these two categories are the particular field of view chosen for display Fig 1 illustrates the difference with the sector array having a pie shaped field of view and the linear array a rectangular field of view

The field of view obtained through the use of a sector array can be achieved by either mechanical or electrical means

The features which we decided to include through considerable marketing studies of medical needs are listed in table I

A comparison of the tradition real time ultrasound system and our Ultrasound SonoFluoroscopy system is shown in table II reflecting the differences betwee these two types of instrumentation

Some of the major differences of particular interest and having a dramatic effect upon the instrument s resolution and diagnostic capabilities are TV format display as this permits an expanded grayscale display and smaller dot size an electronic beam resolution control which allows the operator thru electronic focusing to optimize the beam s resolution at the depth of the tissue under study The variable grayscale dynamic range control allows the operator to optimize the instrument s grayscale processing for the particular patient organ or diagnosis required The multiple modes of operation give the instrument added flexibility for different types of ultrasound applica tions without the necessity of additional instrumentation

Our approach to satisfying the listed features was achieved with the Sono-Fluoroscope I

A closeup of the front panel and operator controls is shown in fig 4

The special importance of some of the specific features of the SonoFluorosco-pe I are explained in greater detail in the reminder of this paper
Fig 5 is a demonstration of the resolution capability of the instrument as i relates to line density

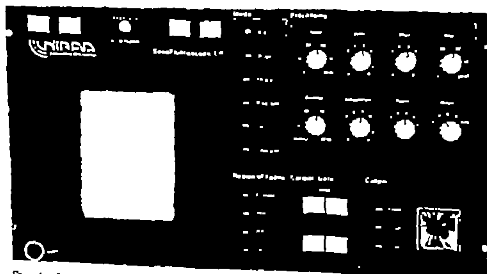


Fig 4: SonoFl

Table 1

SONOFLUOROSCOPE I
FEATURES

1 Television Format High Resolution Monitor

2 128 Line Resolution Display and Photography

3 Optional B-scanner Interface for Post Data Processing

4 Ultrasound Fluoroscopy Image and A mode or complete TGC or ECG displayed

5 Optional Time Motion Electronic Calipers Cardiac Gate and future developments

6 Electronic Beam Resolution Control (Electronic Beam Focusing)

7 Selectable Greatone Dynamic Range from 5 db to 40 db

8 Outline Processing

9 Wide Selection of Transducers Size and Frequency

10 Portable and Modular

Table II

FEATURE COMPARISON
RECTANGULAR FIELD OF VIEW UNIT

FEATURE	REAL TIME	SONOFLUOROSCOPE I
Display	X-Y Monitor - 120 Line Display (60 Lines of Information)	Television Monitor (360 Lines of Image Information)
Gain	Variable Gain Control	Calibrated Control 2 db steps 0 to 50 db
Time Gain Compensation	Far and Near Adjust No visual interpretation of settings	Standard 3 calibrated controls Initial Slope and Delay with visual interpretation on display
Resolution Control (Dynamic Focus)	None	Standard (Operator Adjustable
Electronic Calipers	None	Option
Variable Transmit Power	None	Standard
Time Motion/ECG	None	Option
Frame Freeze	None	Standard
Dynamic Greatone Range	20 db	Variable 5 to 40 db
Video Outputs	Optional with T V Camera	Standard
B scan Interface	None	Option
T V Display	Optional with T V Camera	Standard

focal zone as a function of depth in each study An example of this would be the variance between pediatric and adult cardiology However due to the physical size and cost of linear arrays it is not feasible to have a different transducer for each desired focal zone This implies that it would be desirable to have electronic focusing which could be varied by the operator But first let s look at some of the benefits of focusing and optimizing the arrays

1 Improved Resolution
2 Increased Sensitivity Without Incrasing Power Output
3 Increased Signal to Noise Ratio
4 Decrease Off Axis Lobes
5 Increase Angle of Off Axis Lobes
6 Increase Dynamic Range
7 Instrument Adjustment Less Critical

The SonoFluoroscope I includes a multiple focal zone transducer array which allows the operator to electronically adjust the focal zone without having to change the transducer

The following 3 sketches reflect the dramatic improvement achieved through optimum transducer design and electronic focusing on both transmit and receive

Fig 7 demonstrates the difference in off axis lobes and the main beam width The improvement in decreasing the off axis lobe and decreased beam width is visualized by the operator in the dynamic range and lateral resolution capabilities of the instrument

Fig 8 is a composite representation of the beam pattern of the main beam for different sensitivity ranges of 0 to 6 db 6 db to 12 db and 12 db to 18 db Through focusing each of these ranges has been decreased in width

Fig 9 reflects the difference in the beam shapes due to focusing and variable focus The shaded areas represent the portion of the beam where the lateral resolution s less than 5 mm. Since focusing is so important why doesn t all the instrumentation include focusing on both transmit and receive? The answer is complexity as shown in the fig 10 which indicates the instrumentation degree of complexity required to achieving variable focusing on both transmit and receive as is done with the SonoFluoroscope I W th this type of instrumentation an individual preamplifier transmitter and receiver is required for each individual element of the array along with multiple delays to allow and compensate for the variable focal zones

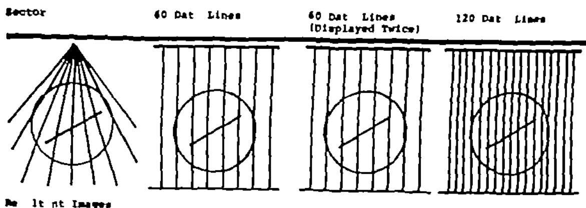


Fig 5 Line density/resolution

It is easy to see the loss in resolution as a function of depth with the sector array system due to the corresponding increase in line spacing The difference in the diagnostic capability of a system including only half the number of data lines and the loss in resolution if the data lines are repeated twice with a simple offset for display is also shown

Fig 6 is a theoretical representation of the different echo amplitudes received from the body during different examinations

The total dynamic range required in order to display all the existing data is approximately 40 dB However the particular examination may only require a small range of these echo amplitudes This indicates the need for a variable dynamic range control so the operator can optimize the instrument s dynamic range for the patient organ or particular diagnosis required In addition to the variable dynamic range control the SonoFluoroscope I includes an edge enhancement control which allows the operator to enhance the organ outlines or vascular structure to facilitate any particular diagnosis

With the standard ultrasound systems employing the single element transducers the operator usually changes the transducer for each patient to optimize the

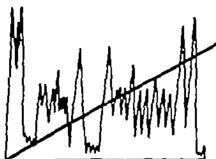


Fig 6 Echo amplitude dynamic range

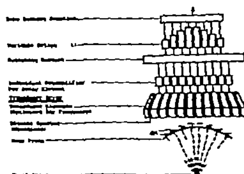


Fig 10: Focus (transmit and receive

Thus far only the improvements obtainable thorugh electronic beam focusing has been discussed Lets look at the difference between the single element transducer and any Phased Linear Array as shown in fig 11 The standard single element transducer has a symmetrical beam pattern while the linear array has two different dimensions of lateral resolution Through electronic beam focusing the beam width in the X direction can be optimized to virtually the same as that obtainable with the focused single element transducers However the Y dimension of the beam is directly related to the width of the transducer element which is optimized for the particular frequency of operation Therefore even through the resolution of a linear array can be dramatically improved it still does not have equal lateral resolution when compared to the single element traditional instruments With the difference in resolution ca pabilities it may be worthwhile also to compare some of the other advantages

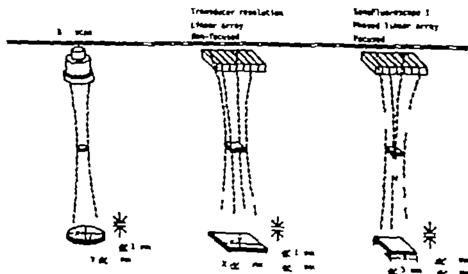


Fig 11

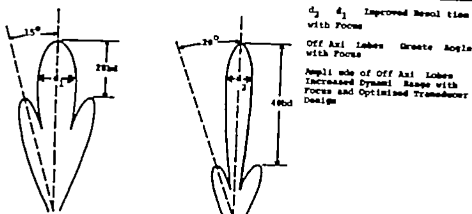


Fig 7 Off ans lobes

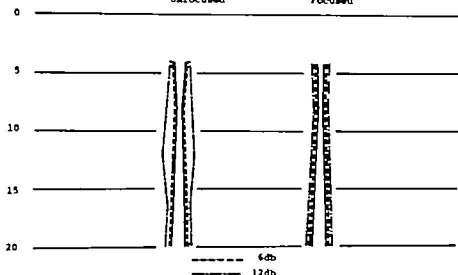


Fig 8 Beam pattern focused vs unfocused.

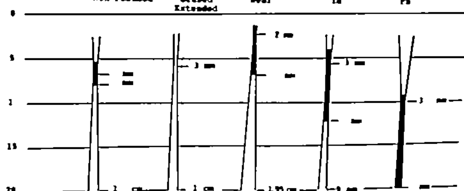


Fig 9 Electronic beam resolution control for X Y5 MHz array

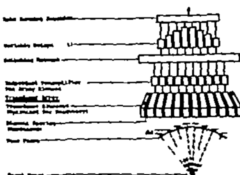


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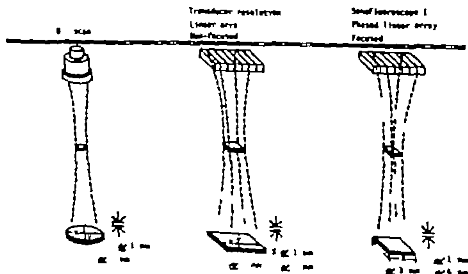


Fig 11

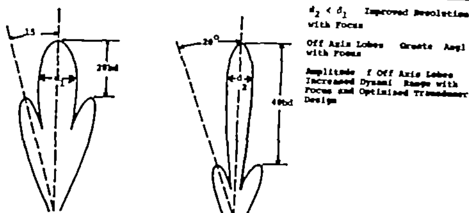


Fig 7 Off axis lobes

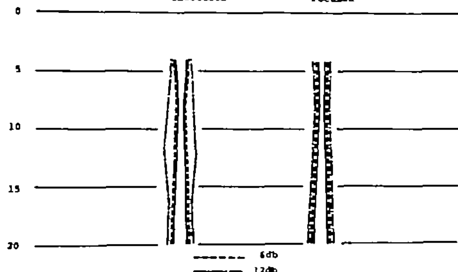


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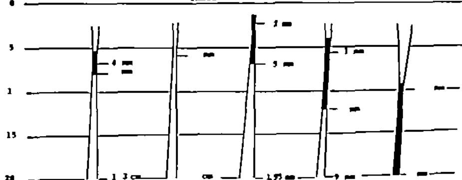


Fig 9 Electronic beam resolution control for 8 85 MHz array

PHASED ARRAY CARDIAC IMAGING: SYSTEM OPERATION RESULTS AND CLINICAL ROLE

J A KISSLO

From the Department of Medicine Cardiovascular and Clinical Cardiology Laboratories Duke University Medical Center Durham North Carolina.

ABSTRACT

Proper clinical use of real-time two-dimensional echocardiography depends upon three major factors: the clinical questions posed of these imaging devices the interrelationship of this technique with other imaging techniques and the quality of the ultrasonic image The Duke experience with this technique has been primarily based on results obtained with a focused phased array imaging system over the last three years During this period of time we have observed that high-resolution cross-sectional ultrasonic images of cardiac structures provide unique diagnostic information that is not possible by any other method Similarly this type of information allows the clinician to pose new questions concerning the use of diagnostic ultrasound in patient care Improvements in image quality that have accompanied the addition of new scan formats and a broad-band transducer have enhanced the clinical reliability of diagnostic information

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Since the work of Edler and Hertz in 1954 (1) M-mode echocardiography has assumed a critical role in the clinical decision making process in patients with cardiovascular disease With the recent advent of techniques for real time cross sectional imaging of cardiac structures the diagnostic capability of ultrasonic methods has been further enhanced

One new imaging method empolys phased array principles to electronically rather than mechanically sweep the ultrasound beam through a given cross sectional field of view This report describes the basic clinical operating characteristics of these focused phased array imaging devices In addition the genereal clinical role of real time two-dimensional echocardiography is discussed

of the different types of ultrasound instrumentation The distinct different advantages of the B Scanner and Ultrasound Fluoroscopy type of instrumentation are shown below

B SCAN ADVANTAGES

1 *High Resolution*
2 Full cross section image
3 Tracks body contour
4 Multiple Greyscale (Processing (WDR NDR VDR)
5 Compound Scan
6 Post Data Processing
7 *Anatomical Reference*

ULTRASOUND FLUOROSCOPY ADVANTAGES

1 *Rapid localization*
2 Tracks moving structures
3 Portable
4 Decreased examination time
5 Less Technique involved
6 Synchronized Photography

The advantages of the standard Time/Motion Cardiology Instrument would be similar to those of the B-Scan device with the exception of storage and dis play capabilities Both the standard B Scan or Cardiology Instrument and the Ultrasound Fluoroscopy Instrument have their place in the present ultra sound department with neither instrument being replaced by the other Rather they complement each other to optimize *the department s diagnostic* capability and efficiency We have carefully studied the ultrasounds community s requirements for Ultrasound Fluoroscopy and feel that the SonoFluoro scope I will play a major role in the future of diagnostic ultrasound

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METHODS

Patients

Ultrasonic images presented herein are from among the first 3 000 patients examined with this system Patients underwent echocardiographic examination for a variety of clinical problems including rheumatic valvular congenital atherosclerotic and other forms of heart disease During these phases of initial clinical trial a variety of scan formats (e g varying sector arc width and line density) transducers and display and recording devices were utilized and thus account for variations in image quality presented

Echocardiographic imaging system

Two dimensional echocardiograms were performed on all patients using a previously described (2 3) real-time phased array imaging system The system uses a handheld 32 element transducer array that measures 14 x 24 mm at the site of skin contact and relies upon phased array principles to electronically steer and focus the sound beam through the structures under investigation Real-time cross-sectional images of cardiac structures are presented in a circular sector format 50 60 or 90 degrees in azimuth at a frame rate of 30 per second A schematic diagram of the transducer and sector arc is shown in fig 1 Images are permanently recorded on videotape for later playback and analysis

This prototype imaging system is undergoing continual midifications in an effort to improve system performance image quality and clinical capability

It is important to note that much detail is lost in the single frame scan images that constitute the illustrations in this paper They were made from the videotape recordings by means of a 35 mm photograph of the sector arc in the stop-frame mode As such there is a loss of visual integration of motion that normally accompanies real time playback More-over there is a severe degradation in image quality caused by photographing a single frame image from the videotape recording because of the fact that an individual vi

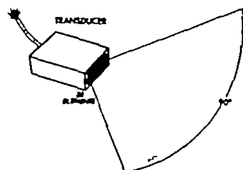


Fig 1 Schematic diagram showing transducer and 90 degree scan plane

deotape frame represents the scan information collected in only 1/60th of a second When operating in the 90 degree 160 line format therefore each single frame video field shows only one half (80 lines) of the information provided in the real time scan

Additional images were obtained since December 1976 using a commercial pro totpye of this imaging system (Grumman Health Systems RT-400) This system is capable of producing cross sectional cardiac images in a 70 degree sec tor arc Basic operating characteristics are similar to those previously described

Examination Technique

Ultrasound examinations were performed with the patients in the supine or left lateral positions The transucer is placed over an aquasonic gel inter face to the left of the sternal border between the second and fifth ribs and costal cartilages An identical acoustic window to that used for time-motion examination of the heart is then utilized Most favorable images of course are recorded when the transducer is held over an intercostal space rather than over the ribs costal cartilages or sternum

A standard echocardiographic examination is performed in a number of cross sectional planes through the heart (fig 2) Position I reveals images through the long axis of the left ventricle (aortic root aortic valve left atrium mitral leaflets and the left ventricular cavity) Position II reveals portions of the right atrium tricuspid leaflets and right ventricle in long axis Serial cross sectional images through the short axis of the heart are then made Position III is through the short axis

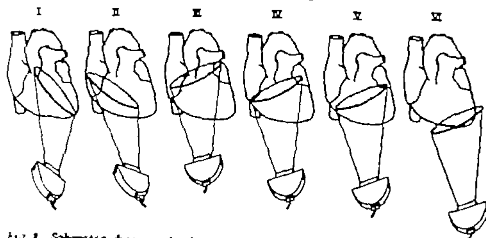


Fig 2 Schematic diagram showing six basic planes for two-dimensional echocardiography See text for details (Reproduced with permission, Circulation 5 : 62 1978)

of the great vessels and atria usually at the level of the aortic valve Position IV provides an image through the short axis of the left ventricle at the level of the mitral orifice Position V provides a short axis view of the left ventricle at the level of the papillary muscles whereas position VI is a similar view at the level of the left ventricular apex

As chest wall configuration and intrathoracic heart position are quite variable from patient to patient a study is initially begun by locating the aortic root mitral valve and portions of the left ventricle in long axis (position I) From that point the remaining cardiac structures are then located by manipulating the transducer into the previously described position II-VI and other appropriate intermediate positions

There is no current standard for the orientation of two-dimensional cardiac images Earlier photographs presented in this manuscript will be oriented with the patient s chest wall to the left More recent images will be oriented (as in M-mode echocardiography) with the chest wall at the top

RESULTS

This section describes several representative scans from patients undergoing examination with these prototype imaging systems Fig 3 shows an early scan from the Duke system through the long axis of the aortic root and left ventricle (Position I) More recent scans through the long axis of the aortic root and mitral valve are seen in fig 4 Normal mitral systolic coaptation is seen in Panel A and compared with two



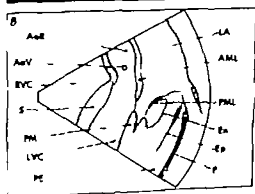


Fig 3 Panel A shows a photo from a stop action video tape frame through the long axis of the left ventricle (Position 1) The aortic root is at the top of the scan and the left ventricular body toward the bottom The chest wall is at the left Note the pericardial effusion AoR = aortic root AoV = portion of aortic leaflets in diastole RVC = right ventricular cavity S = interventricular septum PM = papillary muscles LVC = left ventricular cavity PE = pericardial effusion LA = left atrium AML = anterior mitral leaflet PML = posterior mitral leaflet EN = endocardium EP = epicardium and P = pericardium (Reproduced with Circulation 53 262 1976)

Fig 4 Systolic frames in the long axis of the mitral valve (Position I) The chest wall is at the left Panels A and B show a normal mitral valve Panels C and D show mitral prolapse with predominant anterior leaflet involvement Panels E and F show prolapse with more symmetrical involvement of anterior and posterior mitral leaflets AoR = aortic root LA = left atrium AML = anterior mitral leaflet PML = posterior mitral leaflet LV left ventricle

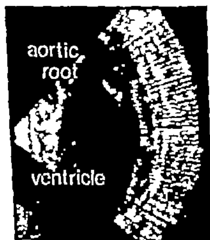


Fig 5 Long section of the left vent ricle (Position I) The che t wall is to the left The ventricle is dilated.

variants of mitral prolapse in Panels C (anterior prolapse) and E (combined leaf let prolapse) The configuration of mit ral prolapse pictured in Panel C is quite common in patients with atrial septal defect (4) Echocardiographic and angiographic comparisons of mitral pro lapse would indicate that two-dimensional echocardiography is a much more sensitive method for detecting mitral prolapse than angiography or M-mode echocardiography (5)

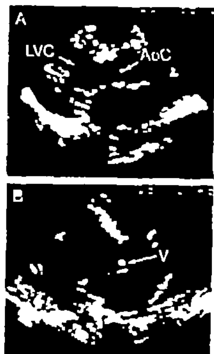


Fig 6 Two patients with similar long axis views of the left ventricle in isometric contraction The chest wall is at the top AoC = aortic cusps LVC = left ventricular cavity V = vegetation Panel A shows the aortic cusps closed in presystole Panel B shows a small vegetative mass

A markedly enlarged left ventricle is see in long axis in fig 5 The 90 degree sect arc allows for visualization of most of t left ventricle despite its marked dilatat Similar views of the long axis are shown i fig 6 The heart in Panel A is captured i isovolumic contraction with the aortic and mitral valves in the closed position The photograph in Panel B shows a scan of a different patient at a similar time in the cardiac cycle The bright target below the aortic valve was documented at surgery to a bacterial vegetative mass Real time tw dimensional echocardiography has been show to be a sensitive method for locating and sizing bacterial vegetative masses (6 7)

Serial short axis scans through the left ventricle at the level of the papillary mus les (Position V) are seen in fig 7 A norma patient in Panel A is compared to one with severe left ventricular hypertrophy (Panel and one with marked ventricular dilatation (Panel C) The high resolution of the dynam cally focused phased array system is seen in the details of endocardial trabeculations in all three patients

Two-dimensional echocardiographic devices ar useful for imaging pathologic problems hitherto impossible to detect by any other technique The scan in fig 8 (Position V) is from a young girl with a severly dilated lef ventricle A large bacterial vegetative mass is seen on the endocardial surface of the in ferior wall of the left ventricle This mass

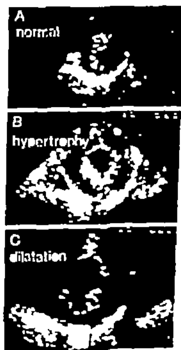


Fig 7 Short axis views of the left ventricl (Postion V) in three patients The chest wal is at the top Panel A is normal Panel B shows ventricular hypertrophy and Panel shows ventricular dilatation Note the deta l of endocardial trabeculations seen in all thr cases

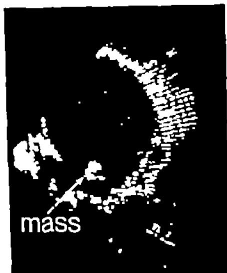


Fig 8: Short axis (Position V) of a patient with large vegetative mass on the endocardial surface

was undetected by conventional M-mode echocardiography and angiography

Several studies have been conducted in this laboratory into the utility of real time two-dimensional echocardiography for the detection of abnormal left ventricular geometry One such detailed study showed this method to compare quite favorably to angiography for the detection of ventricular asynergy Fig 9 shows a left ventricular short axis (Position V) of a patient with severe pulmonary hypertension (Panel A) that resulted in compression of the left ventricle The companion angiographic views reveal a dilated poorly contrac

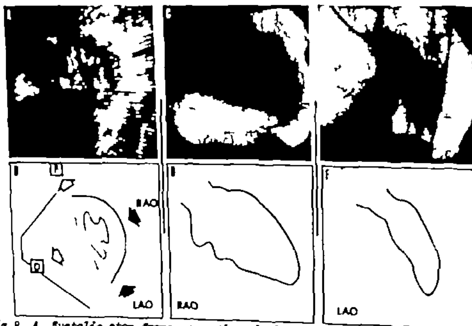


Fig 9 A Systolic stop-frame image through the short axis (Position V) of the left ventricle in a patient with pulmonary hypertension. The chest wall is at the left The ventricle is somewhat flattened in comparison to the normal seen fig 4 C B Schematic diagram of the scan image showing the orientation of the radiographic planes of view Because the ventricle is flattened it appears lightly dilated and poorly contract le in the RAO angiographic projection (C and D) while it is narrow and well contractile in the LAO projection (E and F) Both angiographic frames are in systole (Reproduced with permission Circulation 53 134 1977)

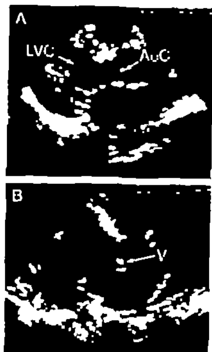


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Two-dimensional echocardiographic devices are useful for imaging pathologic problems hitherto impossible to detect by any other technique The scan in fig 8 (Position V) is from a young girl with a severly dilated left ventricle A large bacterial vegetative mass is seen on the endocardial surface of the inferior wall of the left ventricle This mass

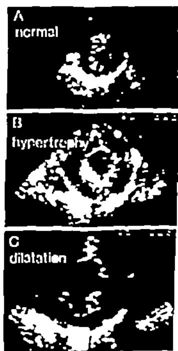


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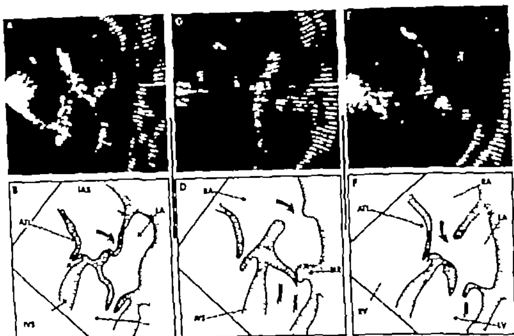


Fig 11 Systolic frames in the long axis of the tricuspid valve and interatrial septum (Position II) The chest wall is at the left Panels A and B are from a normal subject Arrow in B indicates the area f the foramen ovale Panels C and D are from a patient with an ostium secundum atrial septal defect Arrow in D indicates the area of the septal defect Panels E and F are from a patient with an ostium primum atrial septal defect Arrow in F indicate the area of the septal defect ATL - anterior tricuspid leaflet IAS - interatrial septum IVS interventricular eptum; RA = right atrium; MR - mitral ring RV right ventricle other abbreviations as in fig 4

(Position II) in a normal patient (Panel A) a patient with a secundum atrial septal defect (Panel C) and a patient with an ostium primum atrial septal defect (Panel E) Although the sensitivity of these imaging systems for detecting patients with atrial septal defect is as yet unknown (4) these photos prompt hope in this possibility

DISCUSSION

Since first clinically used in 1954 (1) time motion echocardiography has justifiably enjoyed wide clinical application in the diagnosis of a variety of cardiac disorders It cannot be assumed however that a one-dimensional echo image of a moving heart is a completely fair representation of the de tails of cardiac anatomy or motion Indeed there are two basic reasons to believe otherwise First angiographic studies into the complexities of left ventricular contraction clearly indicate that the left ventricle undergoes sequential contraction manifest by a series of rotational and other three

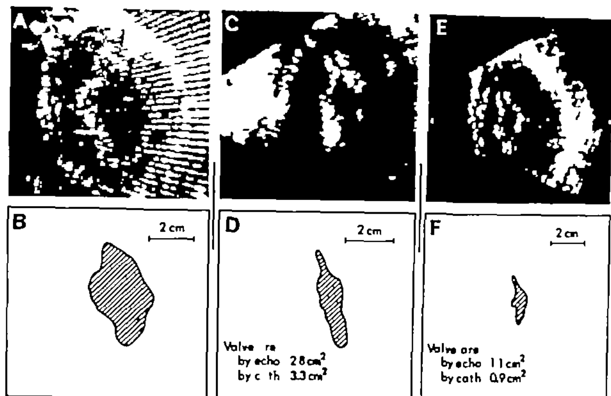


Fig 10 Panel A shows a diastolic frame through the short axis of the left ventricle in a normal individual (Position IV) The chest wall is at the left Note the round contour of the left ventricular wall and the tips of the mitral valve leaflets (anterior on the left posterior on the right) within the left ventricular chamber Panel B schematically shows the area between the leaflets Because this area does not represent the mitral valve orifice normally it was not planimetered Panel C shows a short axis diastolic frame in a patient with mild mitral stenosis Note the thickening and irregularity of the mitral leaflets and the fusion of the commissures Panel D schematically shows the mitral valve orifice area of this patient Panels E and F are comparable to panels C and D for a patient with severe mitral stenosis Note the irregular slit-like orifice

ting ventricle in the RAO view (Panel C) and a narrow vigorously contracting ventricle in the orthogonal LAO view (Panel E) Thus distortion of the ventricle as determined by echocardiography due to pulmonary hypertension may result in an erroneous impression of poor ventricular performance if only single plane RAO angiography is used at catheterization

This method of imaging is also useful for evaluating the severity of mitral stenosis (9) Short axis scans through the level of the mitral orifice (Position IV) are seen in fig 10 Panel A shows a normal orifice while Panels C and E show progressive degrees of mitral stenosis

Because of the wide sector arc and spatial relationships of ultrasonic targets these systems are suitable for the evaluation of substernal targets such as tricuspid valve and interatrial septum Fig 2 shows scans through the long axis of the right ventricle tricuspid valve and interatrial septum

Second the use of other diagnostic techniques such as cineangiography or radioisotope methods will aid in defining the clinical role of each method The geometric configuration of the short axis of the left ventricle seen by echocardiography in fig 9 was a significant aid in interpreting the cineangiographic information

Third continuing development and use of two-dimensional echocardiography has shown progressive advances in image quality parameters such as resolution and gray scale As imaging systems have evolved more accurate target information has become available It is reasonable to believe that as this process continues new and reliable applications of cross sectional echocardiographic information will become available

ACKNOWLEDGMENT

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dimensional movements It is difficult to imagine that data derived from a one dimensional echo recording faithfully reflects these complexities of motion Second while it is possible to obtain useful information concerning intracardiac spatial relationships by sweeping the ultrasound transducer from structure to structure from a relatively fixed position on the chest wall it cannot be assumed that these time-motion recordings represent a true picture of the spatial relationships between the targets The resulting images are of course distorted by both the time it takes to perform the sweep and the changing transducer to target distance

Real-time two-dimensional echocardiography extends the use of M-mode for evaluation of the heart by providing spatial relationships to cardiac ultrasonic target information The specific advantages of the focused phased array approach are the wide field of view relatively small and easily manipulable transducer high resolution and computer controlled scan format The latter capability provides for easy interchange of transducers and scan format in order to maximize image quality These systems are unfortunately not presently suited for examination of neonates or small infants Narrow near field aperture impaired resolution within the proximal 3 cm and transducer ring down artifact all contribute to this problem

In just over three years of clinical use at the Duke University Medical Center in excess of 3 000 patients have been examined for a variety of côngenital and valvular or other acquired cardiac problems Although the present clinical demand for two-dimensional echocardiographic examinations exceeds M-mode by 25% it is proper to think of the two techniques as complimentary The M-mode records one-dimensional sonic information in time Certain observations such as the rapid oscillations of the mitral valve in aortic insufficiency or timing of valvular or heart wall movements with the cardiac cycle are much easier made by M-mode On the other hand the spatial characteristics provided by two dimensional echocardiography give a unique view of cardiac anatomy and provide clinical information that is difficult or impossible to obtain by other methods

To define the clinical role of two-dimensional echocardiography one must examine three basic points First recognizing the advantages and limitations of this tool the echocardiographer must seek unique diagnostic applications of the technique Appreciation of the ventricular endocardial mass in fig 8 is one such application

Second the use of other diagnostic techniques such as cineangiography or radioisotope methods will aid in defining the clinical role of each method The geometric configuration of the short axis of the left ventricle seen by echocardiography in fig 9 was a significant aid in interpreting the cine angiographic information

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THE CLINICAL UTILITY OF TWO-DIMENSIONAL ECHOCARDIOGRAPHY

H RAKOWSKI * R P MARTIN J W FRENCH AND R L POPP

From the Division of Cardiology and Pediatrics Cardiology Stanford University School of Medicine Stanford California

When in 1954 Edler and Hertz first described the use of high frequency ultrasound to record cardiac motion (1) even the most optimistic observer would have found it difficult to predict the consequences of this innovation Initial applications of the technique included the non invasive diagnosis of mitral stenosis (2) pericardial effusion (3) and atrial myxomas (4) As the clinical usefulness of M-mode echocardiography has grown it has played an ever increasing role in the assessment of cardiac disease (5 6)

The development of two-dimensional echocardiography represents a major step in the evolution of ultrasound as a diagnostic tool The greatest advantage of two-dimensional echocardiography is that it permits the correct identifi cation of the spatial orientation of cardiac structures throughout the cardiac cycle This is due to the ability to image the heart in long axis and multiple short axis planes with a wide field of view The information provided is similar to that obtained at cardiac angiography with the advantage of clearly visualizing valvular structure and motion

At the Stanford University Medical Center for the past 18 months we have used a prototype and more recently a production model of the Varian V 3000 phased array ultrasonic sector scanner This system utilizes a hand held 32 element transducer which is focused at 7 cm by an acoustic lens The echo beam is electronically steered through an 80 degree sector arc with a maxi mum recordable tissue depth of 21 cm An M-mode printout can be obtained from any sector line using a movable cursor The method of obtaining studies using a wide-angle phased array system has previously been described (7) Since the same physical properties of ultrasound apply to both M-mode and two-dimensional echocardiography patients with thin chests and without chest wall deformity yield high quality studies using either technique

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In patients such as those with obstructive lung disease in whom it is dif ficult to obtain a standard study additional acoustic windows such as the cardiac apex and subxyphoid area can be used more effectively since the orientation of the echo beam is known With two-dimensional echocardiography useful studies therefore can be obtained in almost all patients

Studies are recorded on videotape for playback and analysis The optimal method of analyzing abnormalities of temporal motion of cardiac structures is at real time or slow motion speed The quantification of parameters such as left ventricular volumes ejection phase indices and valve areas is made using stop-action single fields of a two field/frame video image The illust rations used in this article were taken from stop-action video fields using a Polaroid camera Since with this method all of the information present in one video frame is not being displayed there is some degradation of picture quality In addition it is difficult to adequately display abnormalities that primarily involve the motion of cardiac structures

We will now briefly focus on the initial clinical applications of two-dimen sional echocardiography Besides providing unique information about cardiac structure and function it has been particularly valuable in explaining many of the patterns seen on M-mode echocardiography

ISCHEMIC HEART DISEASE

The ability of wide-angle two-dimensional sector scanning to assess left ventricular dysfunction is more fully described in an accompanying paper Segmental wall motion abnormalities can readily be detected by real time ana lysis of both long and short axis sector scans (8) The site and extent of left ventricular aneurysms can be determined in a manner similar to angio graphy (9 10) In addition to the qualitative assessment of wall motion ab- normalities currently semiquantitative measurements of left ventricular volumes and ejection phase indices can be made regardless of the presence of left ventricular asynergy A potentially important role of two-dimensional echocardiography is the serial non-invasive determination of left ventricu lar function following medical interventions such as afterload reduction or surgical interventions such as coronary artery bypass grafting While the left main coronary artery can often be visualized by two-dimensional echocardiography (11) in our experience the presence of significant proxi mal stenosis cannot reliably be predicted

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and short axis planes respectively The systolic anterior motion present on M-mode studies appears to be due to systolic anterior motion of the lower one-third of the mitral valve and/or chordae tendinear Following septal myectomy the area of muscle removed can be seen as a defect in the septum and the effect of surgery on the degree of systolic anterior motion and the dimension of the left ventricular outflow tract can readily be determined

In patients with restrictive cardiomyopathy due to cardiac amyloidosis the findings are similar to those seen on M-mode studies (13) The left ventricle is symmetrically thickened with normal or decreased volume and the septum is akinetic with little or no systolic thickening Pericardial effusion and/or thickening may also be present

PERICARDIAL EFFUSION

Echocardiography is the simplest and most sensitive means of detecting the presence of pericardial effusion (3) Two-dimensional echo studies in patients with pericardial effusion (fig 2) have demonstrated several points (14) Most effusions first start as collections of fluid in the pericardial space at the level of the mitral annulus This explains why M-mode studies in patients with minimal effusions sometimes reveal an echo-free space at the level of the mitral valve but not at the level of the left ventricular study As the effusion enlarges its distribution may not always be symmetrical and there may be pooling of fluid medially or laterally With sitting or standing the distribution of the fluid is more apical Loculated effusions can more readily be recognized by two-dimensional echocardiography than by M-mode We are currently studying the usefulness of two-dimensional echocardiography during pericardiocentesis to visualize the exploring needle

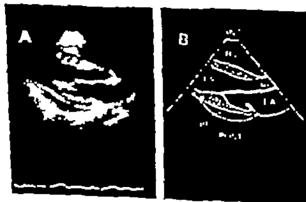


Fig 2: Panel A is a top-action frame taken in the long axis plane with panel B the accompanying line diagram A moderate size posterior pericardial effusion is seen. PE – pericardial effusion other abbreviations as in fig 1

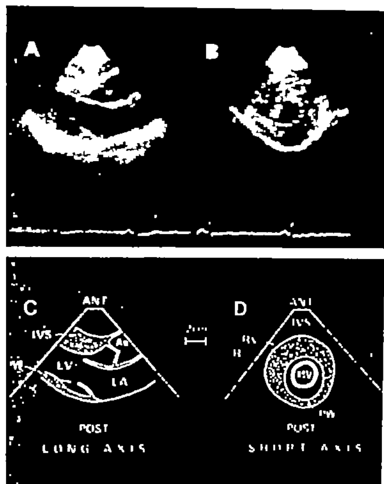


Fig 1 Panels A and B are diastolic stop-action frames taken in the long axis and mitral short axis planes from a patient with idiopathic hypertrophic subaortic stenosis (IHSS) Panels C and D are corresponding line diagrams The degree and extent of asymmetric septal hypertrophy is assessed from analysis of both views ANT = anterior POST = posterior R = right L = left IVS = interventricular septum PW = posterior left ventricular wall LV left ventricle RV = right ventricle Ao = aorta LA = left atrium MV = mitral valve

CARDIOMYOPATHIES

In patients with congestive cardiomyopathy a dilated heart with global hypokinesis is generally seen The closed mitral valve leaflets assume a more vertical orientation due to ventricular dilatation The increased leaflet reflectance and the systolic layering of mitral echoes often seen on M-mode examination appears to be due to inadequate lateral resolution of the echo beam with different parts of the leaflets recorded in the same apparent plane In severe cases all cardiac chambers are enlarged there is little left atrial emptying and the ejection fraction is low

In patients with idiopathic hypertrophic subaortic stenosis (see fig 1) Martin et al (12) have shown the usefulness of two dimensional echocardiography Interventricular septal thickness can more reliably be defined with better localization of the right side of the septum than with M-mode methods Septal thickness may vary from the level of the mitral valve to the level of the standard M-mode left ventricular study and care must be taken to standardize the site of measurement Besides defining increased septal thickness the length and width of the abnormality can be determined from long

separation seen by two-dimensional echocardiography is a semiquantitative estimate of the severity of the stenosis(19) As well stenosis due to valve doming can be detected whereas it is usually missed on M-mode studies (19) Two-dimensional echocardiography may also be more sensitive and specific than M-mode echocardiography in the detection of valvular pulmonary stenosis (20)

The presence of valvular regurgitation is suggested by the same criteria used on M-mode examination (5 6) Two-dimensional echocardiography is particularly useful in determining the cause of non rheumatic mitral regurgitation In patients with mitral valve prolapse two major abnormalities contribute to the prolapsing of the mitral leaflets posterior to the level of the AV groove These are 1) mitral leaflet redundancy with systolic superior arching into the left atrium (21 22) and/or 2) abnormalities of posterobasal left ventricular and mitral annular motion resulting in apparent loss of systolic support for the mitral leaflets (22) The systolic anterior motion of the anterior mitral leaflet sometimes seen in this condition appears to be due to systolic anterior motion of chordae tendineae Ruptured chordae tendineae flail leaflets and mitral annular calcification or thickening can also be detected sometimes with better reliability than on M-mode studies

INTRACARDIAC MASS LESIONS

Two-dimensional echocardiography can be used as an alternative or adjunct to cardiac angiography in selected patients with intracardiac masses (23) When an intracardiac mass is seen differentiation between lesions such as cardiac tumors clots or vegetations often cannot be made and the echo findings must be correlated with the clinical setting This technique is supe-

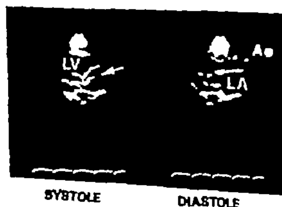


Fig 4: The left and right panels are stop-action frames taken in systole and diastole respectively A large mobile mitral valve mass secondary to infective endocarditis is seen (large arrow Left panel) Abbreviations as in fig 1



Fig 3 Panels A and B are stop-action frames taken in the long axis plane in systole and diastole respectively in a patient with mitral stenosis Note the very dilated left atrium The anterior (upper white arrows) and posterior mitral leaflets (lower white arrows) are thickened The anterior leaflet is tethered at its distal end but is relatively mobile at its mid portion as shown by its anterior diastolic doming (upper white arrow panel B) Panel C was taken in the short axis plane at the level of tip of the mitral valve Again the thickening of both leaflets can be appreciated The mitral orifice is well visualized (white arrow panel C) and is small and irregular Abbreviations as in fig 1

and to monitor the withdrawal of the pericardial fluid

VALVULAR HEART DISEASE

One of the most promising early applications of two dimensional echocardiography has been the assessment of mitral stenosis (15 17) Recent studies have shown that the mitral diastolic EF slope does not correlate well with mitral valve areas determined by the Gorlin formula (16) Two-dimensional echocardiography provides a more direct measurement of mitral valve area in that the mitral valve orifice can directly be recorded in the short axis plane (fig 3) A number of authors using this technique have reported good correlations with the Gorlin formula (15 17) and in some patients cardiac catheterization can be avoided Information about the degree of valvular calcification and/or thickening and valve mobility can also be obtained (16) However certain potential sources of error must be recognized (18) Very irregular mitral orifies and the presence of marked valvular calcification may make it difficult to accurately recognize mitral orifice boundaries In addition limitations in lateral resolution may prevent the precise calculation of small orifice areas (18)

With aortic stenosis aortic valve areas cannot be calculated in the ame manner a mitral valve areas since the aortic valve orifice is usually not fully visualized Weyman has shown that in children the degree of aortic cusp

cardial cushion normally the tricuspid valve is situated to the patient s right and inserts more apically than does the mitral valve With ventricular inversion since the atrioventricular (AV) valves are also inverted the tricuspid valve again inserts more apically but now is seen to the patient s left (25) In patients with AV canal there is absence of the endocardial cushion and therefore a common level of AV valve insertion (25) Absence of the interventricular septum with a common ventricle can also be appreciated (25) Large ventricular septal defects may be seen as defects in the interventricular septum however smaller defects can often be missed depending on their size and location It is disappointing that despite good visualization of the interatrial septum it is difficult to correctly predict the presence of secundum atrial septal defects Many normal patients may have dropout of interatrial septal echoes and therefore one must still rely on the features of right ventricular volume overload to suggest the diagnosis

Transposition of the great arteries (TGA) is best assessed in the short axis plane at the level of the great vessels Normally in that plane the aorta is seen as a central circular structure with the right ventricular outflow tract and proximal pulmonary artery seen as a sausage-shaped structure curving around the aorta anteriorly
In patients with TGA both great vessels are seen as circular structures with the aorta being anteriorly placed (26 27) Occasionally this latter pattern may be encountered in patients without TGA and it is therefore useful to try and follow the anterior vessel to its bifurcation establishing it as the pulmonary artery (25) Other conotruncal abnormalities can also be detected With Tetralogy of Fallot an enlarged right ventricle with overriding of the aorta is seen and in some patients the ventricular septal defect and pulmonic stenosis may be detected With double outlet right ventricle no great vessel can be seen originating from the left ventricle in any view (25)

The rapid peripheral intravenous injection of normal saline through a narrow bore needle produces highly echo-reflective microbubbles that can be followed through the venous circulation (28) Using this technique the presence of right to left shunting can be detected and its level determined particularly using the apical four chamber view Prolonged reflux of microbubbles across the tricuspid valve often implies tricuspid regurgitation



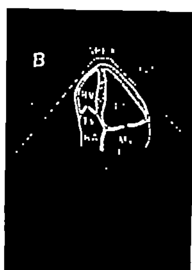


Fig 5 Panel A is a stop-action frame taken in the apical four chamber plane and demonstrates a normal study Panel B is the corresponding line diagram TV = tricuspid valve IAS= interatrial septum other abbreviations as in fig 1

rior to M-mode echocardiography and even cineangiography in the detection of small mass lesions We have surgically confirmed the detection of intracardiac tumors as small as 1 cm (23) In patients with infective endocarditis (fig4) it is valuable to serially follow changes in vegetation size as well as to monitor cardiac chamber size and left ventricular performance Increase in vegetation size or cardiac decompensation while on appropriate medical therapy probably warrants early surgical intervention

Great care must be taken to avoid overdiagnosis Experience aids in the distinction between what is clearly abnormal and what is artifact True mass lesions should be detectable in both long and short axis planes and their exact position localized The presence of significant valvular calcification or reverberations from prosthetic valves may make it difficult to determine whether mass lesions are present The intraoperative insertion of sutures or patches may make it difficult to distinguish postoperative superimposed clot unless serial changes can be demonstrated Left atrial clots cannot reliably be detected and artifacts may sometimes be seen in normal patients although usually they are seen in only one plane True atrial myxomas can be recognized by the fact that the great majority can be shown to attach to the interatrial septum in either the short axis or apical four chamber view

CONGENITAL HE

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cardial cushion normally the tricuspid valve is situated to the patient s right and inserts more apically than does the mitral valve With ventricular inversion since the atrioventricular (AV) valves are also inverted the tricuspid valve again inserts more apically but now is seen to the patient s left (25) In patients with AV canal there is absence of the endocardial cushion and therefore a common level of AV valve insertion (25) Absence of the interventricular septum with a common ventricle can also be appreciated (25) Large ventricular septal defects may be seen as defects in the interventricular septum however smaller defects can often be missed depending on their size and location It is disappointing that despite good visualization of the interatrial septum it is difficult to correctly predict the presence of secundum atrial septal defects Many normal patients may have dropout of interatrial septal echoes and therefore one must still rely on the features of right ventricular volume overload to suggest the diagnosis

Transposition of the great arteries (TGA) is best assessed in the short axis plane at the level of the great vessels Normally in that plane the aorta is seen as a central circular structure with the right ventricular outflow tract and proximal pulmonary artery seen as a sausage-shaped structure curving around the aorta anteriorly
In patients with TGA both great vessels are seen as circular structures with the aorta being anteriorly placed (26 27) Occasionally this latter pattern may be encountered in patients without TGA and it is therefore useful to try and follow the anterior vessel to its bifurcation establishing it as the pulmonary artery (25) Other conotruncal abnormalities can also be detected With Tetralogy of Fallot an enlarged right ventricle with overriding of the aorta is seen and in some patients the ventricular septal defect and pulmonic stenosis may be detected With double outlet right ventricle no great vessel can be seen originating from the left ventricle in any view (25)

The rapid peripheral intravenous injection of normal saline through a narrow bore needle produces highly echo-reflective microbubbles that can be followed through the venous circulation (28) Using this technique the presence of right to left shunting can be detected and its level determined particularly using the apical four chamber view Prolonged reflux of microbubbles across the tricuspid valve often implies tricuspid regurgitation

CONCLUSION

Two-dimensional echocardiography is still in its infancy It has been available only for a short period of time and its use has been confined to a limited number of laboratories Despite this two-dimensional echocardiography has already been established as an important diagnostic tool with widespread clinical application Its potential is truly exciting However the enthusiasm generated by this new technique must be tempered by the knowledge of its pitfalls and potential limitations While the technique is non invasive a good deal of harm can result from erroneous diagnosis The method is used optimally when addressing a specific clinical problem Conclusions should be drawn only when good data are available for analysis Therefore the practitioner must compulsively try to obtain the highest quality studies possible This can only be done if one is familiar with the basic principles of two-dimensional ultrasound has a clear understanding of three dimensional cardiac anatomy and has the technical proficiency gained only by doing a large number of studies The ability of obtain accurate quantitative data may be limited by inappropriate methodology inadequate lateral resolution the level of gain settings the presence of valvular calcification and obliquity of the scanning echo beam to the true plane desired

Again it must be remembered that the technique is still young Improvements in instrument design resolution capabilities and image processing will lead to even more precise information Its full potential has not yet been defined Exciting new areas of investigation include the combined use of transcutaneous Doppler ultrasound and two-dimensional echocardiography to determine cardiac flow (29) Also sophisticated computer analysis of returning echo signals may provide important clues to underlying tissue histopathology (30) The future of two dimensional ultrasound appears bright indeed

ACKNOWLEDGEMENT

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TECHNICAL ASPECTS OF SINGLE TRANSDUCER ECHOCARDIOGRAPHY

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SUMMARY

In echocardiographic recordings optimal amplification and A-mode control should be used In wall motion analysis greater accuracy is obtained by utilization of enlarged display scale When these technical aspects are taken into consideration accurate and reproducible recordings are obtained

INTRODUCTION

In echocardiography the investigator has to know the chief principles of registration construction of his equipment as well as the basis of piezoelectric physics in order to understand the sensitivity of recordings Moreover one has to know the actual sizes of the anatomical sites from which he is recording being aware of the beam width and lateral dispersion of the ultrasonic beam used

Accurate measurements of the anatomical structures are obtained using optimal amplification as well as A-mode control in directioning the beam The accuracy of the measurements when utilizing enlarged display scale will also be greater than by 1 1 scale

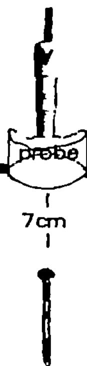
By proper beam selection enlarged scale optimal amplification and utilization of A-mode control recording the left ventricular regional wall motion from several anterior and posterior left ventricular wall locations which cover almost the entire left ventricle is possible

BEAM SELECTION

The shape of the ultrasonic beam can be influenced in order to improve the scanning accuracy and to obtain more distinct M mode recordings from predetermined target areas The divergence in the smaller transducers can be diminished by collimating or focusing the ultrasound beam Wide and or colli

position (x,y) changed by 3mm steps

registrated central and disperse echoes from a nail top in 10 step grid



0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0
0	0	1	3	10	[illegible]	2	0	0	0
0	0	4	20	35	33	13	1	0	0
3	2	6	55	41	42	36	2	0	0
0	0	9	24	47	47	32	2	1	0
0	0	7	30	45	44	36	6	1	0
0	0	0	1	30	37	16	2	0	0
0	0	0	0	1	2	1	0	0	0
0	0	0	0	0	0	0	0	0	0



Fig 1 Demonstration of the absolute intensities of a 2 MHz plane transducer ultrasound beam when the probe was moved by a micromanometere in 10-step grid to and fro over a head of a nail in water bath The recorded intensities are tabled on the left Below the actual values of intensities are drawn the intensity curves of the axial beam The slight lateral dispersion of this wide transducer is easily deleted by reject set

mated transducers are convenient i e when recording regional wall motions of the left ventricle as they provide an uniform and wider axial beam

In an illustrative experiment the axial sound intensity and width of the ultrasound beam of a 2 MHz half an inch transducer was recorded using the head of a nail at 7 cm depth as an absolute reflector The intensities of reflections were recorded from each step moving the transducer in a 10 step grid to and fro as well as from left to right over the nail head (Fig 1) It was then possible to draw the transversal intensity curves of the axial ultra sound The lateral dispersion at this depth is also demonstrated which by using proper reject level will be avoided The experiment also illustrates that the axial intensity of the beam of this plane transducer is quite uni formalthough highest in central direction When using a focused transducer the intensity would be even higher in the center while with a narrower trans ducer the lateral dispersion would be greater A half inch plane transducer with a surface area of 1 5 cm^2 and a quite uniform beam intensity is suitable as for example collimated transducers for studying larger cardiac structures e g left ventricular regional wall motion left ventricular diameters left atrium and the mitral valve It provides a greater reference area of selected wall region and is thus more reliable for repeated wall motion studies With a greater axial beam area the same anatomical site is registered with increa sed probability

The narrower and more accurate beam is obtained when the beam is focused by a converging lens These sharper beams are suitable for studying cardiac valves

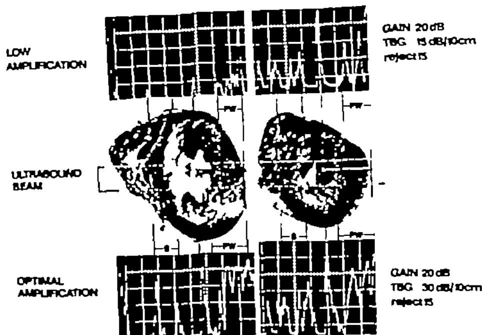


Fig 2 Description of the ltrasound beam traversing two slices of left ventricle when the left ventricular wall echoes were recorded from an autopsied heart in a water bath. The head of a nail fixed to two different positions of the posterior wall was used as reference reflector Formation of the echoes was photoed while the beam was held stationary using low (above) and optimal (below) amplification In contrast to the distinct choes even with low amplification from the smooth septal wall high time bound gain (TBG) is required, in order that both the muscular wall echoes and the trabecular posterior wall echoes are visualized.

Such transducers are usually provided by 5 cm focus radius for children and a 7 5 or 10 cm focus radius for adult studies

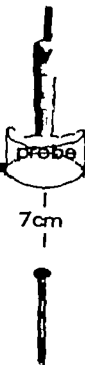
BEAM PROCESSING

The reflected echoes are weak because the difference of propagation impedance of ultrasound from blood to muscle is very small Therefore all echoes require amplification to be visualized

The overall gain with the dynamic range of 0 ton 100 dB usually amplifies all echoes similarly The required overall gain in younger patients is small (15 - 30 dB) but can be twice as high in older subjects with a rigid chest wall (25 50 dB) A larger overall gain is also required in obese patients Because of decibel-wise amplification and attenuation there is remarked difference between anterior and posterior wall echoes approximately from 20 to 30 dB

position (x,y) changed by 3mm steps

registrated central and disperse echoes from a nail top in 10 step grid



0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0
0	0	1	3	10	8	2	0	0	0
0	0	4	28	35	33	13	1	0	0
3	2	6	55	41	42	26	2	0	0
0	0	9	24	47	47	31	2	1	0
0	0	7	10	45	44	36	6	1	0
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0	0	0	0	0	0	0	0	0	0



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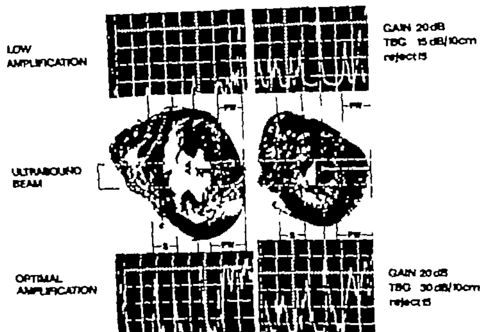


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Fig 3 The effect of time bound gain (TBG) to add the trabecular posterior wall echoes to the myocardial thickness during systole When optimal TBG is utilized reliable values of wall thickness systolic contraction velocity and motion amplitude can be recorded (left) With low amplification (TBG) the trabecular echoes do not appear in diastole but become gradually visible during systole (right) P = papillary muscle T = trabeculation echoes

This difference is corrected by time bound gain (TBG) which is the change of gain with time to compensate for the loss of echo amplitude because of greater attenuation at greater depth The amount of TBG amplification is gradually added up to the overall gain as a function of time The required TBG is usually from 20 to 30 dB over a distance of 10 cm Then despite attenuation it is possible to obtain equally strong anterior and posterior wall endocardial and epicardial echoes (fig 2)

However many spurious echoes arise when maximal TBG is utilized in motion-mode recordings these provoke disturbing lines Therefore conventional echocardiographic equipment are provided by a reject regulator When the reject is used it is important to first recognize the essential echoes so that e g the echoes from the endocardial trabeculations are not deleted The required reject level in adult studies is usually between 5 to 15 dB (fig 1 & 2)

ESSENTIAL ASPECTS IN ECHOCARDIOGRAPHIC RECORDING

In the literature it has been emphasized that the regional wall motion recordings should be characterized by distinct endocardial and epicardial echolines (2) This could be truly achieved if the myocardium were homogenous tissue However the myocardium is constructed of distinct layers and the endocardium is structurally variable the septal part being rather smooth while other areas are heavily trabeculated (7) The epicardial surface is bordered by a more dense epimyocardial layer So in fact a more clear endocardial echo might be seen alone when the gain level is lowered (2) or the reject level is set greater to enable only the strongest echoes to be seen When this was done (fig 3) the posterior wall echoes were formed solely from the thicker trabeculations or from the first muscular layers behind them The echoes from the irregularly rough and rounded trabeculations were weak the ultrasound beam meeting only a small part of the surface of the trabeculae in a straight angle even weaker than the echoes from the first muscular layers behind them (fig 2)

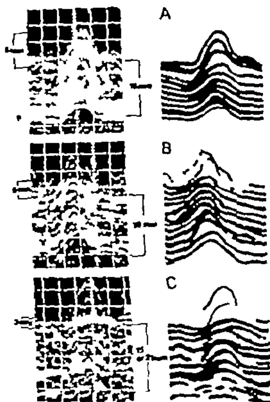


Fig 4: The effect of angulation of the ultrasound beam on the posterior left ventricular wall to measurements of wall thickness and amplitude of motion A In normal perpendicular registration. B In slight angulation the wall echoes are no more moving parallel throughout the systole C In extreme angulation the wall echoes cross each other and the variables are severely altered

With low amplification in the posterior wall recordings the trabeculations cannot be always detected in diastole In systole however the trabeculations squeeze together forming a much denser surface The echoes originating from this barrier will then appear in front of the other endocardial echoes Erroneously high motion amplitudes or systolic wall velocities may then be recorded (fig 3) These difficulties do however not concern the septal part of the left ventricular anterior wall which has a smooth endocardial surface Erroneous resultsin wall motion recordings are also caused by angular directioning of the ultrasound beam towards the wall (fig 4) At an acute angle the wall appears to be thicker since the traversed distance is longer than at straight angle At an acute angle the echoes do not travel parallel but may intersect because of the axial displacement of the systolic summation echoes originating from the muscular layers This unparallel motion of wall echoes is best visualized when a larger display scale is utilized in wall motion recordings (fig 3) Abnormal echo-motion caused by the angulated direction of the probe can be separated distinctly as the A-mode motion pattern is clearly different from normal

The right perpendicular direction of the probe is best achived by slight rotatory movements of the probe in the A-mode control This perpendicular direction is recognized by the maximal amplitude of the endo- and epicardial echoes and the parallel motion of the wall echoes during the cardiac cycle (fig 4) Then

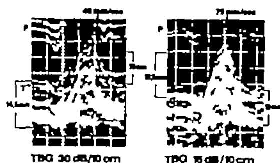


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TABLE 1 PAIRED OBSERVATION REPRODUCIBILITY

Left ventricle	N	Mean	S D of differences	S E	Significance
Diastolic wall thickness (mm)	34	15 4 $\pm$ 1 0	1 2	0 2	NS
Systolic velocity (mm/sec)	33	41 2 $\pm$ 8 5	2 8	0 5	NS x)
	50	29 6 $\pm$ 21 1	5 0	0 7	NS
Amplitude (mm)	35	9 3 $\pm$ 2 1	0 7	0 1	NS
Diastolic diamter (mm)	39	51 8 $\pm$ 4 5	1 8	0 3	NS

x) one month apart

right ventricular junction as well as the apex serve as good anatomical land marks The above technical aspects are also important in cross sectional scannings The advantage of the 2-dimensional real timescanning technique over the single transducer technique is the continuous 2-dimensional visua lization and easy anatomical orientation However in most cases it is diffi cult to obtain distinct recordings with a sector scanner or linear array sys tem The single transducer recordings are still more practical in echocardio-graphic measurements

THE REPRODUCIBILITY OF SINGLE TRANSDUCER RECORDINGS

In order to obtain reliable and reproducible data both for acute studies and follow-up recordings standardized scanning technique utilizing anatomical landmarks is required (4 6)

The reproducibility of single transducer recordings by a standard technique (4) were tested in paired observations performed by the same investigator (table 1) The left ventricular wall motion recordings were obtained varia bly from altogether 8 posterior or anterior wall locations using the echoven triculographic technique (4 5) The posterior and anterior wall motion vari ables as well as the left ventricular end-diastolic diameter were measured from a research series of 39 patients The investigation was repeated after 10 minutes intermission A group of normal subjects belonged to a long term follow-up mate ial and the wall motion was recorded with the same standar dized technique one month apart The standard deviation of differences and the standard error of the differences of the paired observations were small and the t test results nonsignificant (table 1) As a conclusion from this

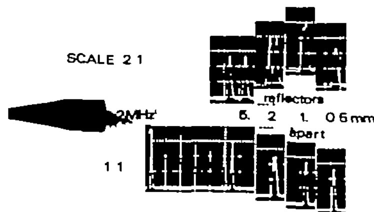


Fig 5 Demonstration of the enhanced scanning accuracy by utilization of enlarged scale Two nails were used as point reflectors at a 5 cm distance from the transducer The returned echoes were registered by 2 1 an 1 1 display scales The point reflectors were set 0 5 1 0 2 0 and 5 0 mm apart By 2 1 scale it is possible to visualize two different echoes when the nails are only 1 mm apart while by 1 1 scale it is not

the true endocardial echoes echoes from the trabeculations are recognized among spurious echoes even when high overall gain is required The A-mode control is best performed in a 2 1 scale (fig 5)

Correlation of the pulsating echo signals to the endocardial och epicardial surfaces can be well seen in the experimental studies and echocardiograms published by Edler och Herz 1961 (1) However the understanding of the behaviour of the A-mode echoes and their importance in echocardiographic recordings have been mainly neglected because of overemphasis of elegant endocardial and epicardial echoes

Another important fact to be borne in mind in echocardiographic recordings of left ventricular motion is the slight antero-apical thrust towards the chest wall and the slight anti-clockwise rotation of the heart during the ejection (3) These changes cause regular disturbance in anterior wall motion recordings seen as broken continuity of the systolic echolines A further physiological abnormality is the rounded paradoxical septal motion observed in sportsmen and in subjects with right ventricular dilatation or volume overload (2) The normal character of the M-mode contraction pattern also in these instances my be recognized as normal systolic thickening

SINGLE TRANSDUCER OR 2 DIMENSIONAL RECORDING

Taken the above technical aspects in consideration it is possible to obtain accurate single transducer recordings of left ventricular anterior and posterior wall motion from precordial sites using a standardized technique (fig 5 fig 1 ref 5) (6) The different regions cover almost completely the left ventricle thus providing us the possibility to map the left ventricular contraction kinetics (fig 1 in ref 5) For 2-dimensional orientation anatomical reference points are needed as such mitral valve leaflets (1) aortic root left and

THE STUDY OF LEFT VENTRICULAR FUNCTION BY M-MODE ECHOCARDIOGRAPHY

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The first use of echocardiography in studying left ventricular function was to measure the cavity size (1 2) and there is a considerable body of evidence to suggest that reliable estimates of a minor diameter can be made using this method More recently a second index of left ventricular function the rate of change of dimension has been studied and taken to indicate fibre shortening rate (3 4) Measurements can be made in absolute terms expressed in cm/sec or normalized to refer to unit length of circumference when they are referred to as Vcf or velocity of circumferential shortening Mean values of shortening rate have been estimated and shown to correlate with corresponding values derived from angiograms in the same patients

The measurements described above are based on only two determinations of cavity size in each cardiac cycle made at end-systole and end-diastole Currently available echocardiographs however have a repetition frequency of 1000/sec and so have the potential of studying wall motion continuously with considerably better resolution in time than that available from angiographic methods Although left ventricular dimension can be measured manually throughout the cardiac cycle this is very laborious and the process can be greatly speeded up using a simple computer technique In order to do this the echocardiogram to be studied is placed on a digitizing table and a cursor is run along each of the echoes to be measured The position of the cursor is detected electronically and converted to a series of digital coordinates up to 100 per cardiac cycle being generated for each echo and stored in the computer This process can be applied to echoes from the right and left sides of the septum the anterior cusp of the mitral valve and endo- and epi-cardial surfaces of the posterior wall It is also possible to digitize any other continuous signal such as the apexcardiogram or the left ventricular pressure trace Once these have been digitized the computer can plot them unchanged or can perform further maneuvres on them For example the coordinates of the septum can be subtracted from those of

experiment the reproducibility of measurements of wall thicknesses and motion amplitudes is less than 1 mm The same is true with left ventricular diameters but with greater individual variation The measurements of the mean systolic motion velocity are subject to greater technical errors in measurement

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The first use of echocardiography in studying left ventricular function was to measure the cavity size (1 2) and there is a considerable body of evi dence to suggest that reliable estimates of a minor diameter can be made using this method More recently a second index of left ventricular func tion the rate of change of dimension has been studied and taken to in- dicate fibre shortening rate (3 4) Measurements can be made in absolute terms expressed in cm/sec or normalized to refer to unit length of circum- ference when they are referred to as Vcf or velocity of circumferential shortening Mean values of shortening rate have been estimated and shown to correlate with corresponding values derived from angiograms in the same patients

The measurements described above are based on only two determinations of cavity size in each cardiac cycle made at end-systole and end-diastole Currently available echocardiographs however have a repetition frequency of 1000/sec and so have the potential of studying wall motion continuous ly with considerably better resolution in time than that available from angiographic methods Although left ventricular dimension can be measured manually throughout the cardiac cycle this is very laborious and the pro cess can be greatly speeded up using a simple computer technique In order to do this the echocardiogram to be studied is placed on a digitizing tab- le and a cursor is run along each of the echoes to be measured The posi tion of the cursor is detected electronically and converted to a series of digital coordinates up to 100 per cardiac cycle being generated for each echo and stored in the computer This process can be applied to echoes from the right and left sides of the septum the anterior cusp of the mitral valve and endo- and epi-cardial surfaces of the posterior wall It is also possible to digitize any other continuous signal such as the apexcardiogram or the left ventricular pressure trace Once these have been digitized the computer can plot them unchanged or can perform further maneuvres on them For example the coordinates of the septum can be subtracted from those of

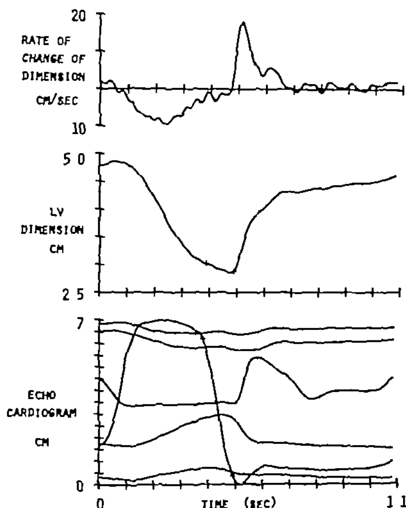


Fig 1 Computer output of left ventricular echocardiogram of a normal subject. The lowest panel represents the digitized data the middle one is a continuous plot of left ventricular dimension and the top shows rate of change of dimension The two crosses represent the timing of aortic valve closure (A2) and mitral valve opening

the posterior wall to give a continuous measure of left ventricular dimension or those of endocardium subtracted from those of epicardium to give wall thickness It is also possible to differentiate a trace with respect to time so that its rate of change can be calculated An example of such a plot taken from the echocardiogram of a normal subject is shown in fig 1 The original information is plotted unchanged in the lowest panel In the middle panel is shown left ventricular dimension which falls during systole and increases rapidly at first during the early phase of ventricular filling and then more slowly during the period of diastasis The timing of aortic valve closure and mitral valve opening are superimposed as two crosses and it will be seen that there has been little change in dimension during isovolumic relaxation It is also apparent that mitral valve opening coincides with minimum dimension suggesting that the increase occurring during diastole is indeed due to ventricular filling Finally the top trace gives the rate of change of dimension which reaches approximately 10 cm/sec during systole and 20 cm/sec during diastole These estimates of peak rates of wall movement have been compared with corresponding values from angiograms in the same patients and satisfactory agreement obtained (5)

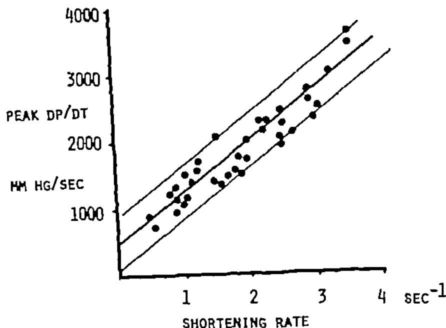


Fig 2 Relation between simultaneous measurements of peak left ventricular dP/dt and peak Vcf in a group of patients with valvular heart disease or cardiomyopathy

Such measurements of peak rates of wall movement appear to have physiological significance The relation between peak normalized shortening rate (peak Vcf) derived from echo and peak left ventricular dP/dt measured simultaneously with a micro- manometer in a group of patients with valvular heart disease or cardiomyopathy is shown in fig 2 which demonstrates strong correlation between them The same relation applies during the immediate postoperative period with such manoeuvres as ventricular pacing or isoprenaline infusion Discrepancies between them occur in the presence of significant mitral regurgitation when peak Vcf is greater than would be anticipated from peak left ventricular dP/dt due to the low impedance pathway for blood flow from the left ventricle If peak rates of wall movement are to be used as a measure of left ventricular function therefore it is necessary to take the load against which contraction occurs into account

During filling measurement of continuous rates of change of dimension has proved of clinical value since the normal pattern is modified in the presence of mitral valve disease (7) In mitral stenosis two abnormalities occur 1 a reduction in the peak rate of increase of dimension to less than 12 cm/sec and 2 prolongation of the period of early diastolic filling measured from the time of minimum dimension to the discontinuity on the dimension

curve representing the onset of diastasis These abnormalities return towards normal after successful mitral valve surgery Since it is not the mitral valve itself that is being studied but rather its physiological effects on the left ventricle the same methods can be applied to patients with mitral prostheses In addition it is possible to detect valve obstruction or paraprosthetic leak (7)

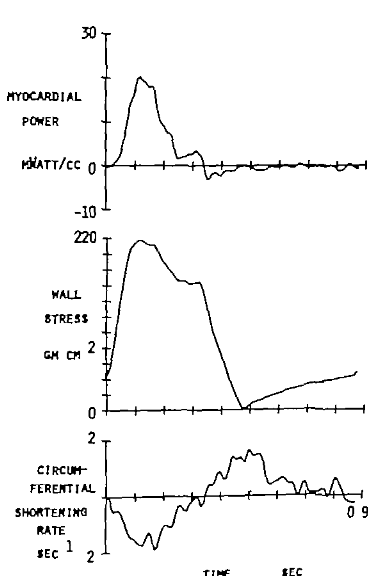


Fig 3 Left ventricular wall stress and shortening rate from a normal subject The top panel shows myocardial power calculated as the product of wall stress and shortening rate

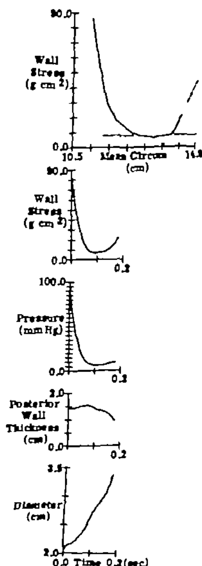


Fig 4 Left ventricular stress-strain relations during diastole zero time corresponds to minimum dimension The lowest three panels show changes in dimension wall thickness and pressure and above this changes in wall stress with time and (top) the stress-strain relation

Abnormalities of wall movement may also occur in hypertrophic cardiomyopathy in some of whom similar patterns to those of mitral valve disease may be seen while in others the pattern of filling is normal or even restrictive in character (8) Identical observations have been made angiographically (9) and both methods show strong correlation between prolonged filling and the presence of angina as a prominet symptom With increasing recognition of the significance of diastolic abnormalities in hypertrophic cardiomyopathy it is likely that further attention will be given to observation of the pattern of wall movement in such patients

The scope of echo methods can be increased by simultaneuosly measuring left ventricular pressure (6) Knowing left ventricular pressure dimension and wall thickness it is possible to derive wall stress continuously throughout the cardiac cycle fig 3 being based on the simple analytical method of Falsetti et al (10) Myocardial power derived as the product of wall stress and shortening rate gives a measure of left ventricular contractile function which takes resistance to shortening as well as peak rate into account Finally left ventricular diastolic stress strain relations can be studied (fig 4) (11) Such methods take changes in wall thickness into account and indicate the complexity of diastolic events even in normal subjects

It seems therefore that the scope of echocardiography in studying left ventricular function can be considerably increased by using a simple computer technique Knowledge of peak rates of wall movement may have appreciable clinical as well as physiological value and with simultaneous pressure measurements a variety of mechanical values can be calculated very much less laboriously than by angiography The presence of incoordinate contraction does not preclude their use which is described in detail elsewhere in this symposium

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INFLUENCE OF PHARMACOLOGIC INTERVENTION AND VALVULAR HEART DISEASE ON LEFT VENTRICULAR EJECTION PHASE INDICES A REVIEW

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ABSTRACT

Echocardiography represents an established noninvasive technique to evaluate left ventricular (LV) performance The LV ejection phase indices may be divided into three categories: (1) volume-dependent (2) circumferential and (3) wall thickening Since the latter two are not volume dependent they are clinically more useful in patients with dilated left ventricles These parameters have limited clinical value in the presence of left-sided volume overload conditions (e g mitral regurgitation and aortic regurgitation) since significant LV dysfunction may exist in the presence of normal ejection phase indices by echo The echocardiogram is also a sensitive procedure to detect subtle alterations in LV function following acute or chronic interventions with various types of vasoactive and inotropic drugs

Echocardiography has become accepted as a useful clinical parameter for the determination of left ventricular function Although the unique noninvasive features of this method to evaluate left ventricular performance make it attractive certain limitations have been recognized Echocardiographic measurements can be repeated without risk in the same patient as desired and the ventricular volume and function indices can be followed serially through the natural course of the disease Even though the accuracy of echo techniques has been well established the methods are less reliable when the left ventricle has been dilated or when areas of segmental wall motion disorders coexist (3 5 11 12 30 31 34 36)

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tion of LV volume by echocardiography (34) The final equation was

$$V \left[\frac{7\ 0}{2\ 4 + D}\right] D^3$$

where V volume

and D international dimension measured by echo

Because of the non-uniform contraction of the left ventricle in patients with ischemic heart disease as well as the variations in the relationship between the major and minor axis diameters Lalani and Lee from Canada selected a different method to measure cardiac output from the echocardiogram (26). These investigators determined cardiac output by measuring the cross-sectional area of the aortic root X left ventricular ejection time X mean aortic flow velocity X heart rate They reported this method of derivation to correlate well with Fick determined outputs in the same group of patients Ejection time is measured from the aortic valve and the systolic closure (A wave to C point) of the anterior mitral valve leaflet was assumed to represent the mean aortic flow velocity One potential source for error exists since M-mode echo equipment is not capable of displaying simultaneous recordings from both aortic and mitral valves It must also be remembered that this technique is based upon all patients having normal aortic and mitral valves

Gould and associates from Seattle Washington have provided a better explanation of contraction of the intact ventricle (19). Their study described the basis for the method to use angiography to quantitate the three separate contributions to overall ventricular performance; namely longitudinal shortening circumferential shortening and systolic wall thickening These investigators observed the contribution of each directional component to the total power developed by a mid-wall equatorial element of myocardium to be (1) longitudinal 14% in normal and diseased ventricles (2) circumferential 45% in normal increasing to 55% in dilated ventricles and (3) wall thickening 40% in normal decreasing to 31% in dilated ventricles

By conside ing these components to overall LV performance as proposed by Gould et al it contributes to a better understanding of the numerous echocardiog aphic parameters which have been employed to evaluate LV function

Although the estimation of left ventricular (LV) muscle mass does not represent one of the ejection phase indices alterations in mass may influence LV performance Some investigators have found a good correlation between angio and echo derived LV mass (36) Recently Doctors Devereux and Reicheck from the University of Pennsylvania have challenged the standard methods for determination of LV internal dimensions posterior wall thickness and ventricular septal thickness (8) These investigators reported a better correlation with postmortem anatomy by excluding the thickness of left septal and posterior wall endocardial echo lines in the LV internal dimension The determination of left ventricular wall stress has traditionally required angiographic and left ventricular pressure measurements Brodie and associates from the University of North Carolina have reported a combined hemodynamic echocardiographic technique to measure left ventricular meridional wall stress throughout the cardiac cycle (4). Having validated the accuracy of this technique by comparison with angiographic data these investigators cited the potential advantages including the ability to study wall stress continuously and to assess its response to serial interventions

The accuracy and reproducibility of determining ventricular wall thickness and mass by echocardiography has been established (36) The major problem in the calculation of left ventricular volumes by the conventional M-mode technique is that only a single dimension is employed to calculate the volume of the three dimensional left ventricle Two potential problems arise in the clinical situation where heart size and performance may be altered (1) the various formulas which can be applied to determine volumes are less accurate for enlarged ventricles than for normal size hearts and (2) localized areas of wall motion disorders may not be seen or if observed quantitating the effect of these segmental abnormalities upon overall performance may be extremely difficult Pombo and associates from the Univeri sity of Alabama employed the cube method to determine ventricular volumes (30). These investigators noted good correlation by angiography and echocardiography in the assessment of LV volumes and end diastole stroke volume and ejection fraction Other investigators have noted a poor correlation between angiographically and echocardiographically determined volumes in patients with left ventricular asynergy (34). Doctor Teichholz observed the relationship of minor and major axes of the left ventricle over a wide range of volumes to derive a theoretically corrected equation for determina

tion of LV volume by echocardiography (34). The final equation was

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By considering these components to overall LV performance as proposed by Gould et al it contributes to a better understanding of the numerous echocardiog aphic parameters which have been employed to evaluate LV function

There is no way to measure the minor contribution of longitudinal shortening by M-mode echocardiography Fortunately 85 90% of LV performance can be measured by determining circumferential shortening and wall thickening both of which can be determined by the echocardiogram very well For the purpose of this presentation I will divide the echo-derived measurements of LV function into three categories

(1) Volume-dependent indices such as percent ejection fraction (%EF) and stroke volume (SV)
(2) Circumferential indices which includes the mean rate of circumferential shortening (V_{CF}) and percent fractional shortening (%FS)
(3) Wall thickening indices which includes the percent systolic thickening of both septum and posterior wall (%WT_S %WT_{PW}) the velocity of contraction of both walls (V_S V_{PW}) and the normalized velocities of the walls

$$\left[V_S(\text{sec-1}) \quad V_{PW}(\text{sec 1}) \right]$$

Numerous investigators have studied LV performance in the presence of mitral and aortic valve disease (1 2 16 20 22 23 28 29 33 37) The echocardiogram has been utilized not only to evaluate ventricular function in these patients but also to assess the severity of the valvular disease

Because of the inherent difficulty in consistently recording the valve orifice area in patients with aortic stenosis wall thickness and LV function indices have been studied by echocardiography in order to estimate the severity of the obstruction This has been potentially very important since no other noninvasive technique is capable of reliably predicting the degree of aortic stenosis nor accurately detecting progression of the obstruction without serial cardiac catheterizations (13) Hirschfeld and associates from the University of Cincinnati observed significant shortening of the isovolumic contraction time in children ages 5 to 19 years with aortic stenosis compared to normals (20) McDonald reported limited value of certain echocardiographic measurements in 31 patients with aortic stenosis but no associated heart failure (28). Two categories of LV function volume dependent and circumferential indices were normal in these patients Only after LV failure had occurred did the %EF V_{CF} and %FS decline significantly Of those parameters measured the only abnormality observed in these patients prior to [illegible] increased thickness of the posterior wall

When the stenosis was mild the wall thickness remained normal; a 20% increase in diastolic wall thickness occurred in those with moderate stenosis and a 44% increase in LV posterior wall thickness was found in patients with severe stenosis (aortic valve area < 0 5 cm^2)

Bennett et al reported an increased end-systolic wall thickness which was proportional to the intraventricular pressure in patients with aortic stenosis (2). The relative wall thickness was determined from the ratio between echocardiographic measurements of end systolic posterior wall thickness and cavity transverse dimension These investigators derived values for LV pressure in patients with aortic stenosis by using the formula

$$\text{Systolic intraventricular pressure (kPa)} \quad \frac{30 \times \text{wall thickness}}{\text{transverse dimension}}$$

Peak systolic aortic valve gradients were determined by substracting the brachial artery systolic pressure derived by sphygmomanometer from the echocardiographic estimates of LV pressure The peak gradients as well as valve areas compared favorably with the same parameters which were measured at cardiac catheterization This approach is based upon the observation that given normal left ventricular function the magnitude of concentric LV hypertrophy is determined by wall stress (wall tension per unit of cross sectional area) with wall mass increasing in proportion to left ventricular load until wall stress returns to normal

Johnson and co-investigators from Children s Hospital in Cincinnati observed echocardiographic findings in 45 children with aortic stenosis and their results varied from data reported by McDonald (23) This group of investigators from Cincinnati found a good correlation between echo-derived percent fractional shortening and valvular gradient measured at the time of cardiac chateterization When the shortening fraction exceeded 40% the LV aortic peak systolic pressure gradient was greater than 45 mm Hg in all patients except one Another circumferential LV function index namely V_{CF} was also found to be increased more than 1 55 circumferences/sec in those patients with valve gradients of 45 mm Hg or more

Glanz and associates employed the methodology of Bennett to evaluate the severity of aortic stenosis in 13 children and adolescents (16). The derived constant (k) was 225 6 7 mm Hg in this group of patients and the correlation (r 0 92 P < 0 001) was excellent between the estimation by echo and the directly measure LV peak systolic pressure

Experience in our own laboratory has also provided additional data which support the clinical value of the methodology used by Bennett to estimate the severity of aortic stenosis However it should be emphasized that these measurements to estimate LV pressure and valve gradient should not be done in the absence of certain clinical history and physical findings Patients with hypertension certain forms of primary myocardial disease and hypertrophic cardiomyopathies may have sufficient wall hypertrophy without LV dilatation to create a misleading suggestion that an aortic valvular gradient may exist

Although there is significant value to be derived from the echocardiogram in judging the severity of aortic stenosis by measuring circumferential and wall thickening indices the LV function indices in patients with aortic regurgitation have not had a corresponding value Both volume-dependent and circumferential LV ejection phase indices by echo correlate very closely with the sameparameters when measured from the LV angiogram in the left anterior oblique position (22) However the same correlation does not exist with the right anterior oblique angiographic data in patients with pure aortic regurgitation The net result is that the ejection fraction fractional shortening and mean circumferential shortening rate all tend to remain normal in spite of LV dysfunction due to severe aortic insufficiency In a few individual cases we have observed minor deterioration of LV function indices in serial studies during a three to four year period However a single echocardiogram has not proven to be very useful in predicting the severity of chronic aortic insufficiency or degree of overall LV dysfunction

The echocardiographic assessment of LV performance in patients with mitral valve disease has been shown tobe normal inmost cases (29 33 37) The left ventricle may be abnormally smallin a few cases of severe mitral stenosis (6 of 47 patients) (29) The ejection phase indices are usually normal in patients with mitral regurgitation even in the presence of left heart failure Accordingly the severity of myocardial impairment may be underestimated by the echocardiogram Some investigators have found the well compensated patients with mitral regurgitation possess supernormal circumferential indices (%FS 40 to 45 and $V_{\overline{CF}}$ 1 5 to 1 6 circs/sec) (33 37).

Doctors Gibson and Brown from London have used echocardiography to measure instantaneous LV dimension and filling rates in patients with mitral valve disease (15) They determined the LV filling rates in normal subjects to be 880 ml/sec with peak filling occurring at .11 sec from onset of diastole

and 45% of the stroke volume had entered the ventricle within that period As expected the filling rates in those patients with mitral stenosis were markedly reduced averaging 210 ml/sec and the filling rates in those with mitral regurgitation were increased to 2 400 ml/sec Furthermore they observed a significant difference in the peak filling rate of patients with aortic insufficiency compared to those with mitral regurgitation Those with aortic insufficiency had slower filling rates approximately 1 600 ml/sec and only 19% of the stroke volume had entered the left ventricle within 13 sec compared to 50% of the stroke volume within 10 sec in those patients with mitral regurgitation

There has been limited clinical application of echocardiography to assess the influence of cardiac drugs on ventricular performance However it has been well established that echocardiography is a sensitive technique to measure acute alterations in LV volume to detect localized changes of wall motion and to evaluate the effects on myocardial performance of various pharmacologic agents (6 9 10 14 17 18 21 24 25 27 32). Redwood and associates observed that LV end-diastolic dimension decreased an average of 11 7% and end-systolic dimension an average of 12 7% following sublingual administration of 0 4 mgm nitroglycerin in normal subjects (32). Tilting the subjects from a supine to an 80^0 head-up position caused comparable reductions in transverse LV dimensions as occurred with nitroglycerin Phenylephrine caused a rise in atrial pressure decrease in heart rate and a significant increase in end-diastolic dimension measured by echo Furthermore these investigators observed no change in the mean V_{CF} by tilting or from phenylephrine but it was increased by nitroglycerin (from 1 3+ 1 to 1 7 1 circ/sec) These data on phenylephrine is in disagreement with later findings reported by Hirschleifer and associates from San Diego (21). These authors noted a significant decrease in mean normalized V_{CF} from 1 38 + 06 to 1 09 + 05 circ/sec ($P < 0\ 001$) in 25 normal volunteers After augmenting the heart rate with atropine administration mean normalized V_{CF} increased from 1 22 0 5 to 1 38 + 06 circ/sec ($P < 0\ 001$) Respective decreases and increases were also noted in the normalized posterior wall velocity measurements following phenylephrine and atropine Accordingly these investigators pointed out that when ultrasound is used for serial assessment of LV performance or monitoring the influence of a given drug both heart rate and systemic arterial pressure must be considered in view of thei independent effect upon LV function

Goldstein et al from London recently reported the value of using nitroglycerin to assess changes in the LV end systolic dimension as an index of

regional performance rather than an estimate of overall LV performance (17) Contraction improved in certain hypokinetic segments and increased systolic shortening occurred during exercise following administration of nitroglycerin Dumesnil and associates from Canada reported similar findings and observed following nitroglycerin that 54 of 103 hypokinetic regions improved (9). These investigators also studied 13 patients after success ful bypass surgery and noted that regional ventricular function had become normal in 11 nitroglycerin responsive areas but failed to improve in 21 nitroglycerin nonresponsive regions

Kerber and co-investigators from the University of Iowa employed ultrasound in open chest anesthetized dogs to assess wall motion disorders produced by coronary artery ligation (24) A significant increase in aneurysmal bulging during isometric contraction occurred with isoproterenol or ouabain admi nistration However during the ventricular ejection phase the mean poste rior wall velocity increased with isoproterenol glucagon norepinephrine and ouabain

The clinical usefulness of echocardiography to evaluate the effects of drugs on left ventricular performance has been further demonstrated by Crawford et al (6) They noted an improvement in the circumferential in dices in normal subjects following longterm oral digoxin therapy An ana logous study was performed by Gomes and associates in 10 patients with alcoholic cardiomyopathy (18). These investigators noted significant im- provement in the mean posterior wall velocity normalized posterior wall ve locity mean circumferential fiber shortening and ejection fraction follo- wing oral digoxin therapy The positive inotropic effect and reduced LV asy nergy in patients having coronary artery disease have been demonstrated by Ferling and associates following rapid intravenous digitalization with oua bain (10)

Evaluating the effects of generel anesthesia on left ventricular function is another new application for the echocardiogram Lendrum et al from Chicago reported significant deterioration of LV performance in children with no heart disease follwing nitrous oxide and Halothane or Ethrane anesthesia (27).

We have recently concluded a study in our laboratory in which we evaluated in a double-blind fashion the acute effects of 10 mgm chewable isosorbide dinitrate (CHIS) in 11 patients with severe chronic left ventricular failure We elected to measure only the circumferential and wall thickening indices [illegible] dependent indices because all patients had signifi

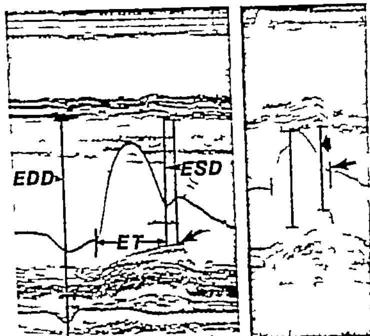


Fig 1 Representative views of the left ventricle with simultaneous carotid pulse recording in two different patients with chronic left ventricular failure showing abnormal septal motion and reduced systolic thickening of the posterior wall in both cases The patient in the right panel has paradoxical septal motion and the most posterior point during systole occurs in early ejection. The arrow pointing to the second line which precedes the incisura represents the measurement position for the end-systolic dimension (ESD) The left panel hows a patient with an akinetic septum dilated left ventricle reduced systolic thickening of the posterior wall with the most anterior peak of the endocardium (arrow) occurring in diastole after the incisura of the carotid pulse The correct measurement site for the ESD is through the incisura. EDD end-diastolic dimension; ET ejection time

cant LV dilatation There was a slight improvement but not statistically significant in the circumferential indices following administration of CHIS However systolic thickening of the posterior wall was significantly increased following the drug Because of the severe LV dysfunction and frequent association of paradoxical septal motion we modified our technique to measure the end systolic dimension The incisura of the simultaneous carotid pulse recording although delayed 20 to 40 msec from actual end systole was a more consistent precise measurement point than either the septal or posterior wall echo reflections Since the peak anterior point of the posterior wall endocardium was not a reliable marker for end systole in fact it can actually occur in early diastole (fig 1) we determined the end systolic dimension to be the sho test distance between endocardial surfaces of the septum and posterior wall timed with the incisura of within 40 msec preceeding it

In conclusion echocardiography represents a useful noninvasive technique to evaluate the effect of various pharmacologic agents on left ventricular performance Furthermore it is obvious that careful attention must be given to proper recording technique controlled studies with reproducible measurements and overall quality control Additional investigations in the field are needed but it does represent an important method to aid the clinician in weighing potential advantages and disadvantages of cardiac drug regimens

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LEFT VENTRICULAR FUNCTION ASSESSMENT BY WIDE ANGLE TWO-DIMENSIONAL ULTRASONIC SECTOR SCANNING

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One of the most promising applications of wide-angle two-dimensional echocardiography is the assessment of left ventricular function The M-mode left ventricular study although useful is somewhat limited by its narrow field of view Good echocardiographic angiographic correlations for left ventricular volumes and ejection phase indices can be obtained only in patients without significant left ventricular asynergy (1 5) While M-mode echocardiography often can detect regional left ventricular contraction abnormalities particularly of the interventricular septum and posterior wall many wall segments cannot be adequately visualized

As described in an accompanying paper a prototype and a production model of the Varian V 3000 80^{0} phased array ultrasonoscope has been in clinical use in our laboratory for 18 months Two-dimensional echocardiography with this wide field of view can provide cross sectional images of the entire long axis of the left ventricle simultaneously Two-dimensional echocardiography also has the unique ability to image the short axis of the heart in multiple planes from the level of the aorta to the cardiac apex In this manner all segments of the left ventricle can be seen with correct spacial orientation

Qualitative Assessment of Left Ventricular Function Left Ventricular Asynergy

In assessing segmental wall motion abnormalities by two-dimensional echocardiography the left ventricle can be divided into five segments the interventricular septum anterolateral wall posterolateral wall inferior wall and apex as shown in Fig 1 Combined assessment of long axis and serial short axis views is made Regional hypokinesis akinesis or dyskinesis can be detected and its severity can be graded subjectively Kisslo has shown good correlation between the angiographic and two-dimensional echocardiographic detection of left ventricular asynergy (6) and we have confirmed

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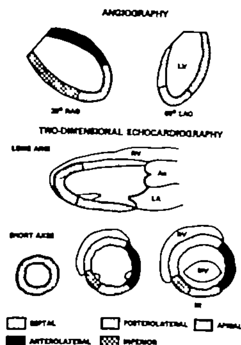


Fig 1 The schema for the correlation of segmental left ventricular contraction abnormalities seen by left ventriculography and two-dimensional echocardiography is shown The short axis views were taken at the level of the left ventricular apex (I) papillary muscles (II) and mitral valve (III)
RAO = right anterior oblique
LAO = left anterior oblique
LV = left ventricle RV = right ventricle Ao = aorta
LA = left atrium MV = mitral valve

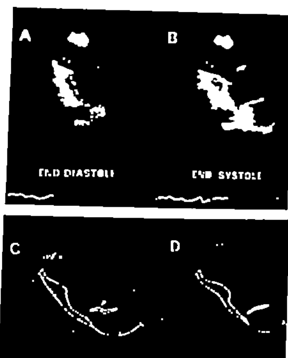


Fig 2 Panels A and B are stop-action frames taken at end-diastole and end-systole in the apical long axis plane The double white arrows point to the large apical aneurysm which has dyskinetic systolic motion Panels C and D are line diagrams corresponding to panels A and B respectively AN = aneurysm PAP = papillary muscle PW = posterior left ventricular wall LA = left atrium AML = anterior mitral leaflet LV = left ventricle

this in our laboratory Since abnormalities of motion are being assessed the optimal method of analyzing these studies is to view them at real time speed It is difficult to display segmental wall motion abnormalities using stop action single-frame images

In patients with ischemic heart disease the development of a left ventricular aneurysm can lead to significant clinical deterioration Since this lesion is potentially surgically correctable its early and accurate detection is of obvious clinical importance In our limited experience two-dimensional echocardiography can accurately define the location and size of left ventricular aneurysms with high sensitivity and specificity This technique has been useful in establishing the diagnosis even when it had not been suggested by physical examination electro(

A characteristic hinge point was seen in the affected segment beyond which there was aneurysmal bulging of the left ventricular wall with dyskinetic systolic motion (Fig 2) Two-dimensional echocardiography also has proved to be as accurate as angiography in predicting resectability of aneurysms in that the degree of involvement of the papillary muscles and basal seg ments can be determined Therefore two-dimensional echocardiography can be used as a reliable non-invasive screening test for left ventricular aneu rysms and is especially useful in patients with minimal indications for angiography

While the detection of asynergy has its greatest clinical application in ischemic heart disease it is also useful in the assessment of other cardiac disorders In patients with idiopathic hypertrophic subaortic stenosis the extent of septal hypokinesis and the effects of myectomy can be deter mined In some patients with mitral valve prolapse abnormalities of posterobasal left ventricular contraction can be detected and their contribution to the M-mode echocardiographic appearance of prolapse can be assessed After aortic valve surgery most patients develop hypokinesis of the interventricular septum Two-dimensional echocardiography allows one to non invasively follow the natural history of this abnormality and detect whether there is late normalization of wall motion

In most patients with global left ventricular dysfunction all segments are seen to be equally hypokinetic Fig 3 is taken from a patient with severe congestive cardiomyopathy following viral myocarditis There is little change in ventricular area from end diastole to end-systole defining the patient s poor ejection fraction



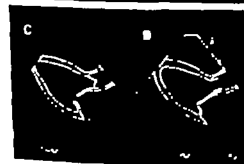




Fig 3 Panels A and B are stop-action frames taken in the long axis plane at end-diastole and end-systole respectively Panels C and D are line diagrams corresponding to panels A and B respectively Note the poor ejection fraction due to the patient s severe congestive cardiomyopathy RV right ventricle IVS = interventricular septum PW = posterior left ventricular wall LV = left ventricle; AML = anterior mitral leaflet; PML = posterior mitral leaflet; Ao= aorta; LA left atrium ECG = electrocardiogram.

Paradoxical Interventricular Septal Motion

Two dimensional echocardiography has given a clearer understanding of the dynamics of paradoxical interventricular septal motion Pearlman (7) has suggested that paradoxical septal motion in the presence of normal ventricular activation is not a diagnostic marker for right ventricular volume overload but merely may reflect right ventricular dilatation relative to the left ventricle from any cause If one assumes that during systole the septum moves toward the center of ventricular mass then the position of the septum at end-diastole determines the direction of systolic motion It at end diastole the septum is posterior to the center of ventricular mass as can be seen with relative right ventricular dilation its systolic motion will be anterior and therefore paradoxical (7) When these patients are studied using two dimensional echocardiography abnormalities of cardiac geometry and septal motion can be seen with correct spatial orientation Normally in the long axis plane a septal hinge point is seen separating a small cranial segment that is neutral or has systolic anterior motion from a much larger caudal segment that has posterior systolic motion Consequently an erroneous diagnosis of paradoxical septal motion may be made on M-mode studies if septal motion is assessed near its attachment to the aortic root In patients with true paradoxical septal motion there is caudal (apical) displacement of the hinge point therefore most of the septum is moving paradoxically in systole (8) When viewed in the short axis plane the septum is flattened and posteriorly displaced making the configuration of the left ventricle ellipsoid rather than circular (9) In extreme cases there may be frank reversal of the normal diastolic septal curvature giving the kidney shaped appearance of encroachment of the septum into the left ventricular cavity In such patients with the onset of systole there is rapid septal eversion toward normal circular shape which causes the rapid early systolic anterior septal motion seen with M-mode echocardiography (9) This is illustrated in Fig 4

Quantitative Assessment of Left Ventricular Function

Superficially it would seem easy to compare two-dimensional echocardiography with angiography and obtain good correlations of quantitative left ventricular function Both techniques provide dynamic images of the whole long axis of the left ventricle Both can display the left ventricle in motion at real time speed or can provide stop-frame images for tracing end diastolic and end systolic ventricular outlines However there are significant differences between the two techniques that limit comparison Angiography provides

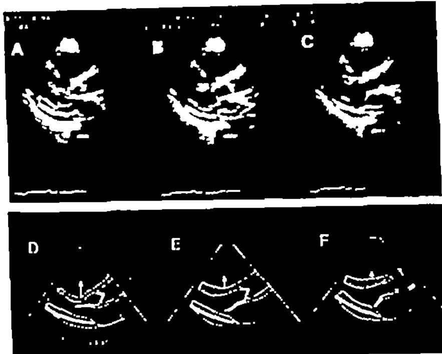


Fig 4: Panels A B and C are stop-action frames taken in the long axis plane from a patient with severe pulmonary hypertension and pulmonary regurgitation. Panels D E and F correspond to A B and C respectively The right ventricle is markedly dilated with a small left ventricular cavity The size of the white arrows indicates the magnitude of paradoxically anterior systolic septal motion still to come Panel A was taken in late diastole I the isovolumic contraction phase (Panel B) the interventricular septum is already rapidly moving anteriorly and most of the paradoxical motion has already taken place by mid-systole (Panel C) An incidental small po terior pericardial effusion is present RV = right ventricle LV left ventricle; IV = interventricular septum; PW posterior left ventricular wall Ao = aorta; LA — left atrium PERI = pericardium EFF effusion*

a silhouette image of the left ventricle and volumes and ejection phase indices are usually measured using a 30^0 right anterior oblique projection In contrast two-dimensional echocardiography provides a tomographic cross-sectional image which should theoretically give a consistently smaller cavity area than a silhouette projection In addition the plane of the cross sectional image of the long axis of the left ventricle is more analogous to a hemiaxial 60^0 left anterior oblique angiographic projection

Certain technical limitations of two-dimensional echo systems also must be considered Left ventricular studies suitable for quantitative analysis can be obtained in only about 80 % of patients Factors such as obesity and chronic obstructive pulmonary disease may lead to incomplete visualization of the left ventricle In some patients the only good echo window is found at or just medial to the cardiac apex The routine use of this apical view maximi

zes the number of acceptable studies and also helps eliminate the foreshor tening of the left ventricle that sometimes can be seen in studies taken from the 3rd and 4th intercostal spaces With certain abnormalities of cardiac geometry (e g left ventricular aneurysm or idiopathic hypertrophic subaortic stenosis) all parts of the long axis of the left ventricle may not lie in the same plane In these patients two dimensional sector scans may underestimate the true long axis area whereas the angiographic silhouette may provide an overestimation There are other potential sources of error as well Significant systolic cardiac motion out of the plane of the scan may occasionally occur so that different parts of the heart are compared in systole and diastole Also since lateral resolution is only 3 to 5 mm apparent boundaries between the left ventricular cavity and walls may not represent the true endocardial interfaces

Despite these potential limitations accurate semiquantitative measurements can be obtained Wide angle two-dimensional echocardiography can clearly define patients with normal versus abnormal left ventricular volumes and ejec tion fractions regardless of whether left ventricular asynergy is present In our experience comparison of quantitative measurements of angiographic and two dimensional echocardiographic data taken from single-plane long axis views of the left ventricle alone do not yield a high correlation It is not yet clear whether accurate quantitative data are obtainable from cur rent two-dimensional echocardiographic studies It may be that the method of extracting it has not yet been perfected The serial short axis views obtai ned with two-dimensional echocardiography provide unique information about the shape of the left ventricle We are currently studying the feasibility of combining data from different planes of the left ventricle as well as using several mathematical models of the left ventricle instead of a simple ellipse of rotation Forthcoming improvements in system signal processing resolution and stop-frame image quality probably also will lead to better quantification of left ventricular function

ACKNOWLEDGEMENT

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METHODS

Patients Left ventricular wall motion was studied by real time two-dimensional echocardiography and biplane cineventriculography in 105 consecutive patients undergoing diagnostic cardiac catheterization for a variety of clinical problems Mean + standard deviation ages was 47 + 11 (range 15 to 72)

Echocardiographic Methods Two-dimensional echocardiograms were performed on all patients using a previously described (1 2) real time phased-array imaging system All two-dimensional echocardiograms were obtained on the day prior to cardiac catheterization according to previously described techniques (2) Cross sectional images of the left ventricle were obtained in the long axis of the left ventricle and in serial short axis views at the levels of the mitral valve tips of the papillary muscles bodies of the papillary muscles and apex

In an attempt to closely approximate the true short axis of the left ventricle the transducer was placed perpendicular to the chest wall and the ventricle was scanned until the image of the left ventricle appeared most circular in configuration Particular care was taken to avoid extreme transducer angulation as it distorted the appearance of the ventricular circumference (oval rather than circular) and made the interpretation of ventricular geometry and asynergy unreliable

Catheterization Methods All patients underwent complete left and right heart catheterization from the right groin using the Seldinger technique Biplane left ventricular cineangiograms were obtained in the orthogonal left and right anterior oblique projections Cineangiograms were recorded on 35 mm film at a speed of 60 frames per second

Data Analysis Ventricular wall motion was classified as either normal or abnormal in each of five echocardiographically and angiographically determined wall regions (anterolateral posterolateral septal inferior and apical) Abnormal systolic wall motion was defined according to the terminology of Herman et al (3) The echocardiograms and cineventriculograms were analyzed by two independent groups of investigators neither having knowledge of the other s conclusions until the time of data correlation To serve as a basis for comparison the echocardiographic results were used to predict the appearance of the biplane cineventriculogram in each patient The echocardiogram was then judged as correct or incorrect in identifying the ventricular wall motion characteristics as determined by angiography In this way a total of 525 potential wall regions were analyzed by each method After initial correlation both echocardiograms and angiograms were reviewed by the combined investigative teams to determine the reasons for agreement or disagreement

EVALUATION OF THE LEFT VENTRICLE BY TWO-DIMENSIONAL ECHOCARDIOGRAPHY

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SUMMARY

Left ventricular wall motion was assessed in 105 consecutive patients both invasively using biplane cineangiography and non-invasively by a real-time phased-array two-dimensional echocardiography system Ventricular wall motion in five anatomic areas of the ventricle (anterolateral posterolateral apical septal and inferior) was analyzed by both methods in a double-blind manner Two-dimensional echocardiographic images were deemed adequate for analysis in 82 % of the regions (430 of 525) Fifty-five discrepancies were noted in the comparison of the remaining 430 regions

The reasons for discrepancies in interpretation between the two methods were established for 54 during retrospective review: 33 were due to echocardiography (inadequate target visualization observer error, or tangential echo views) Fifteen were related to angiography (overlay of silhouettes or observer error) and six were due to other reasons including definition problems or spatial orientation difficulties

Both real-time two-dimensional echocardiography and cineangiography have advantages and disadvantages The techniques used together could provide more complete information concerning ventricular wall movement than is now currently available

INTRODUCTION

Real time two-dimensional echocardiography is a relatively new approach to visualizing cardiac dynamics At present there is little available information regarding the utility of this method for the detection of ventricular asynergy In this study the results of the assessment of ventricular wall motion by two-dimensional echocardiography were compared to similar data obtained by biplane cineventriculography This comparison was used to define the interrelationships between the two techniq

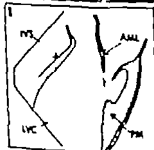


Echocardiographic Angiographic Correlations In all 105 patients biplane ventriculograms were considered adequate for the analysis of wall motion Eighteen percent (95 of 525) of wall regions however could not be visualized by two-dimensional echocardiography It should be noted that in the 430 regions visualized by echocardiography wall motion characteristics were correctly identified in 87% (375 of 430) Discrepanicies between the echocardiographic and angiographic findings occurred in 13% (55 of 430)

Fig 2 Stop-frame mid-diastolic image and schematic diagram through the long axis of the left ventricle in a 90 degree sector arc There is mild ventricular dilatation and virtually the entire left ventricle is seen from aortic root to apex En=endocardium. The remainder of the abbreviations are the same as in Fig 1









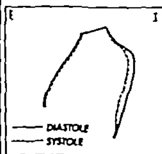


Fig 3. Sequential diastolic (A) and systolic (B) stop-frame scan images in the 90 degree sector arc through the long axis of the left ventricle of a patient with coronary artery disease and a huge ventricular aneurysm. The corresponding schematic diagrams (B and D) have been added Panel E demonstrates diffuse asynergy with relative preservation of motion along the posterior wall region at the base of the heart LVA left ventricular aneurysm. Remainder of abbreviations are the same as in Fig 1

RESULTS

Correlative Examples Figure 1 shows stop frame systolic images through the long axis and two short axis views of the left ventricle from a patient with a normally contracting left ventricle Figure 2 demonstrates the advantage of the 90 degree sector arc since this wide field of view occasionally allowed for visualization of the entire left ventricle in long axis

The two-dimensional echo and angiographic findings of a patient with a ventricular aneurysm are shown in fig 3 and 4 While the two-dimensional echo demonstrated normal wall motion of the posterior region of the heart this was difficult to appreciate in the ventriculogram due to superimposition of the large opacified aneurysm on the remainder of the ventricular silhouette

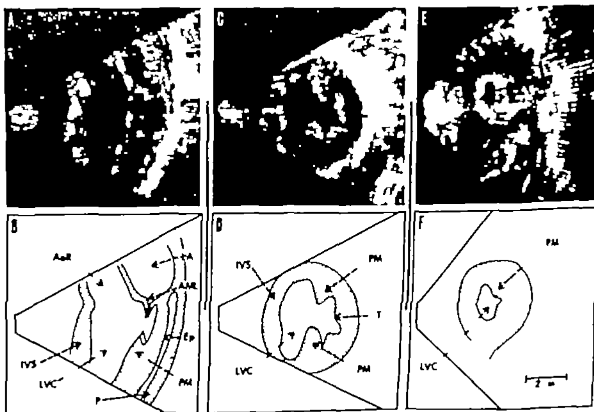


Fig 1 Stop-frame systolic images and schematic drawings through the ventricular long axis (Panels A and B) short axis at the papillaries (Panels C and D) and short axis at the apex (Panels E and F) from a patient with a normally contracting left ventricle and mild mitral prolapse Scans in Panels A and C are in the 60 degree sector arc while the scan in Panel E is in the 90 degree sector arc Note that the left ventricle is normally circular in configuration when viewed in short axis (C and D) Several endocardial trabeculations can also be seen in Panel C AoR = aortic root LA = left atrium AML = anterior mitral leaflet Ep = epicardium PM = papillary muscle P-pericardium LVC = left ventricular cavity IVS = interventricular septum T = trabeculation

includes unresolved disagreements between the echocardiographic and angiographic interpretations The indeterminate discrepancies included only mild abnormalities and in two instances the asynergy noted in a specific region by echocardiography was seen in an adjacent wall region by angiography

Discrepancies due to observer error and inadequate target visualization by echo were most frequently encountered in the interpretation of apical wall motion while problems experienced with the ventricular silhouette on angiography were encountered most frequently in interpreting septal wall motion

Adequacy of Echo Targets ince the double-blind analysis revealed that in adequate endocardial echo targets accounted for the most frequent error by echocardiography the echocardiograms were carefully reviewed in an effort to establish minimal criteria for assessing the adequacy of an echo image Upon review it was clear that at least 50% of the endocardium in any one wall region must be visualized throughout the cardiac cycle in order to reliably predict the presence or absence of asynergy Visualization of all regions of the left ventricle by two-dimensional echocardiography was possible in 60% of these patients while failure to visualize any of the regions occurred in 11% The most readily visualized regions were the septal and posterior walls while the most difficult region to visualize was the ventricular apex

DISCUSSION

Proper echocardiographic technique is most important in obtaining a true cross-sectional image of the left ventricle Even though this difficulty was well recognized before this study was begun 7% of the discrepancies noted on double-blind analysis were due to improper echo technique The heart as a constantly moving three dimensional target is rotating in and out of the interrogating plane during the cardiac cycle An improperly directed transducer causes the scan plane to intercept the ventricular cavity tangentially and may result in distortion of normal ventricular configuration and wall motion When the ventricle is viewed in long axis this problem is most easily recognized when the normal elliptical configuration of the cavity appears circular or cut-off near the origins of the papillary muscles When the ventricle is viewed in short axis this problem is recognized when the cavity appears oval rather than circular in shape

Eighteen percent of the discrepancies noted were due to echocardiographic observer error and resulted from two basic problems that were heretofore unrecognized in the interpretation of two dimensional echocardiographic images

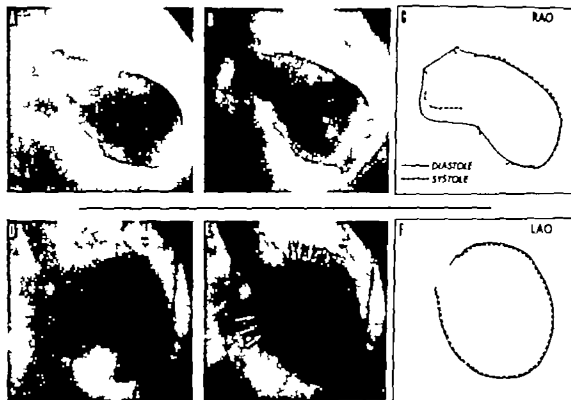


Fig 4 Sequential diastolic (A and D) and systolic (B and E) angiographic frames fromthe same patient pictured in Fig 3 The RAO view is pictured on the top row while the LAO view is on the bottom Note the large ventricular aneurysm and contracting base in Panel C The arrows in Panel E point to the contracting base that is poorly visualized through the silhouette of the aneurysm in the LAO view (Panel F) These findings were similar to those predicated by two-dimensional echocardiography

Discrepancy Analysis In order to fully appreciate the interrelationships between two dimensional echocardiography and angiography the data was then retrospectively reviewed Suspected reasons for 54 of the 55 discrepancies were identified and classified Of the 34 discrepancies attributable to echocardiography ten were due to observer error and 19 were due to inadequately visualized echo targets that were previously judged as adequate Despite the care taken to properly position the transducer on the chest wall four errors were caused by tangential angulation of the transducer through the short axis of the ventricular cavity resulting in distortion of wall movement

The majority of the 15 discrepancies due to angiography resulted from the superimposition of abnormally contracting wall regions over the normally contracting portions of the ventricle (Fig 4) For example when severe anterior wall asynergy was present the abnormally contracting anterior wall was superimposed over the interventricular septum in LAO angiographic view thus obscuring true septal wall motion

The six discrepancies termed indeterminate were so classified because they could not readily be attributed to either imaging technique This category

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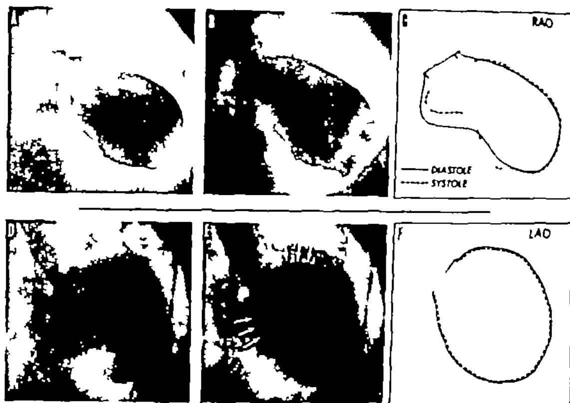


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Since this study deals with the correlation of data from two distinctly different imaging techniques it is not surprising that discrepancies occurred that could readily be attributed to both echocardiography and angiography It is most important to realize that the two techniques working together could potentially provide more complete information concerning ventricular wall movement than is now available

ACKNOWLEDGEMENT

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First as the heart contracts in systole it rotates and moves in an inferior and anterior direction When the left ventricle is viewed in its short axis by echocardiography therefore this systolic descent and anterior motion appeared to reduce the visually apparent posterior motion of the septum induced by ventricular contraction Second several observer errors were made when the 50 degree sector scan format was utilized and the entire ventricular circumference in short axis was not included in the field of view Because of this incomplete visualization the relative motions of the various wall regions were not fully appreciated and failure to recognize minor to moderate degrees of asynergy resulted Although a short axis scan through a normal size ventricle usually includes the entire ventricular wall in a 50 degree sector arc such is not the case when the ventricle is dilated As wide a field as possible therefore should be employed when examining the left ventricle for asynergy

Proper judgment concerning the adequacy of an echocardiographic image for interpretation of left ventricular asynergy is clearly most important since 35 % of the discrepancies noted were due to the inadequacy of the echocardiographic image In retrospect it appeared that assessment of wall motion characteristics of a specific wall region could be reliably attempted only when at least 50% of the endocardium in any one wall region is visualized throughout the cardiac cycle It was encouraging that all five heart wall regions could be visualized using this criterion in 60% of the patients examined It should be kept in mind however that the most difficult wall regions to visualize were the apical inferior and anterolateral Such findings are not surprising since target drop out (loss of targets due to tangential angulation fo the echo beam) and/or interfering lung tissue are most often encountered when attempting to image these specific wall regions

The fact that 27% (15 of 55) of the discrepancies noted were attributable to angiography indcates that cineventriculography as any other technique has certain limitations Paramount among these is the superimposition of the silhouette of an abnormally contracting well segment over one that is normal making detection of the normal motion occasionally difficult or impossible For similar reasons most of the ventricular wall surfaces are inaccessible to radiographic contrast imaging techniques since the only motion detected by this method is on the border of the visualized silhouette Biplane cine ventriculography of course tends to reduce these sources of misinterpretation Since this technique is invasive its application is limited to relatively small numbers of patients selected for cardiac catheterization

subvalvular portion of the ouflow tract (1) In addition outflow obstruction may occur at multiple levels as the common association of coarctation of the aorta and bicuspid aortic valve illustrates (2 3)

Correct characterization of obstruction requires that one recognize the presence and severity of the lesion as well as its location in the outflow tract and morphologic type When obstruction is present at one level it is also important to be able to evaluate the remainder of the outflow tract to rule out associated lesions M-mode echocardiography has been variably suc cessful in detecting the morphologic type extent and severity of lesions producing obstruction to left ventricular outflow (4 5) In some types of obstruction such as IHSS the M-mode technique has been extremely valuable permitting the diagnosis (6 7) severity (8) response to therapy (9) and inheritance pattern of the disease to be examined (10 11) In other areas such as congenital valvular aortic stenosis (12 14) the M-mode technique has been notably unreliable

Much of the difficulty with the M-mode method is due to the tubular nature of the outflow tract The M-mode beam can only reflect obstruction or nar- rowing of this cylindrical structure by recording a change in outflow tract diameter during continuous scanning from one region to another Recording a change in diameter may be difficult to evaluate; however since apparent decrease in diameter may result from eccentric beam angulation while an artifactual increase in diameter occurs when the beam is scanned obliquely along the long axis of the vessel

Cross sectional echocardiography by enlarging our field of vision generally permits the entire area of obstruction to be encompassed within the plane of the scan This allows comparison of the area of obstruction with the more normal outflow tract proximal and distal to this region In addition more precise characterization of the morphology and extent of the lesion and in certain cases its severity is possible In this report we will review our ex perience using the cross-sectional echocardiographic system to detect and characterize areas of obstruction to left ventricular outflow Consideration of these lesions will begin at the superior portion of the outflow tract in the region of the aortic arch and progress down the outflow tract through the region of the aortic valve into the left ventricle

AORTIC OBSTRUCTION

A. Coarctation of the Aorta

It is well established that by placing the M-mode transducer in the supra

CROSS-SECTIONAL ECHOCARDIOGRAPHIC ASSESSMENT OF AORTIC OBSTRUCTION

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SUMMARY

Cross-sectional echocardiographic features of aortic obstruction occurring at multiple levels of the left ventricular outflow tract are discribed Specific pathologic entities considered include coarctation of the aorta supravalvular valvular and discrete subvalvular aortic stenosis as well as functional or idiopathic hypertrophic subaortic stenosis At each of these levels the cross-sectional method permits direct visualization of the obstructing lesion it's morphologic characteristics and extent In addition the relationship of the area of obstruction to more normal surrounding areas of the outflow tract can be assessed Studies at the supravalvular and valvular levels indicate the direct imaging of the stenotic area may permit estimation of severity

At the subvalvular level the patterns of development of functional obstruction can be examined and the mechanisms of this type of obstruction further illucidated Finally in addition to direct visualization of individual areas of obstruction it is possible to detect or exclude areas of concommittant obstruction at other levels of the outflow tract Cross-sectional echocardiography therefore represents a rapid non-invasive method for visualizing the location extent severity and dynamic nature of lesions producing obstruction to left ventricular outflow

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Obstruction to left ventricular outflow may be either congenital or acquired The obstruction may result from a fixed anatomic area of narrowing or be functional varying with the physiologic state of the patient (e g IHSS) Although obstruction occurs most commonly at the level of the aortic valve it may be located in the aorta distal to the valve or in the

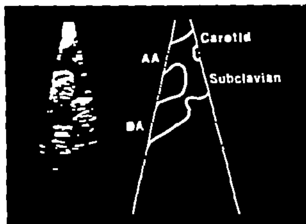


Fig 2 Cross-sectional scan of the distal aortic arch and proximal descending aorta from a patient with coarctation of the aorta There is a localized area of discrete aortic narrowing distal to the origin of the left subclavian artery At the level of maximum obstruction there appears to be almost complete obliteration of the vascular lumen Distal to the area of obstruction the aorta returns to the relatively normal luminal diameter



Fig 3: Angiogram corresponding to the cross-sectional study in Figure 2 In this recording there is again a localized area of constriction or coarctation of the aorta distal to the origin of the left subclavian artery The similarity in appearance of the obstructing lesion by both these imaging techniques is apparent

main relatively parallel throughout the area of the scan In a recent study (18) to evaluate the ability of cross sectional echocardiography to record anatomic changes in the proximal descending aorta in patients with coarctation it was observed that the distal aortic arch and descending aorta could be visualized in 16 of 18 patients examined In each of these 16 patients there was a localized area in which the echoes from the walls of the aorta protruded into the aortic lumen producing partial constriction or obstruction of the vessel In each case there was a similarity between the echocardiographic location and appearance of the lesion and the location and morphology of the coarctation at angiography

Fig 2 is a cross sectional recording from a patient with coarctation of the aorta In this figure there is marked inward bending of the echoes from the medial and lateral walls of the descending vessel distal to the origin of the left subclavian artery This shelf of echoes protruding into the vascular lumen produces almost complete obstruction of the vessel at this level Fig 3 is an angiogram recorded from the same patient demonstrating the presence of an area of coarctation at a level similar to that visualized by the cross sectional recording



Fig 1 Diagram illustrating the position of the cross-sectional probe in the suprasternal notch and orientation utilized to record the aortic arch and proximal descending aorta While recording this region the probe is normally directed inferiorly posteriorly and slightly leftward The plane of the scan is therefore oriented approximately 45° to both the sagittal and coronal planes of the body

sternal notch and directing the beam inferiorly one can record echoes from the superior and inferior walls of the aortic arch the right pulmonary artery and the left atrium (15 17) Visualization of the distal aortic arch and proximal descending aorta and detection of obstruction or coarctation in this region however has not been possible with the M-mode system This occurs because the path of the descending aorta is parallel to or directly away from the ultrasonic beam Because of this orientation the walls of the vessel are poorly recorded and an accurate aortic diameter in this region unobtainable Since detection of areas of obstruction requires comparison of the diameter in the narrowed region with that in surrounding normal areas this inability to accurately record the transverse diameter of the vessel prevents detection of coarctation

Cross sectional echocardiography by displaying the derived acoustic data in a spatially oriented format permits the distal aortic arch and proximal descending aorta to be visualized Since the walls of the vessel can be imaged it is possible to estimate the transverse diameter and hence to appreciate changes in this diameter produced by localized obstruction Fig 1 illustrates the transducer placement and areas encompassed by the 30° sector with the plane of the cross sectional scan oriented parallel to the long axis of the descending aortic arch In normal subjects the descending arch appears as an elongated tubular echo free area which curves leftward and inferiorly away from the scanning transducer The walls of the vessel re-

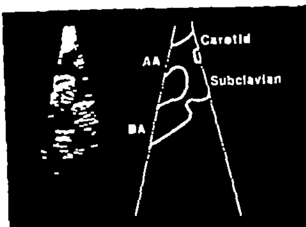


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In addition to the abnormal anatomic appearance of the arch in patients with coarctation there was also a characteristic change in the pattern of systolic pulsation of the vessel which aided in the detection of coarctation With coarctation there was very prominent pulsation of the vessel proximal to the area of narrowing Distal to the area of obstruction the vascular pulsation was markedly decreased Although similar degrees of pulsation of the aortic arch may be seen in patients with aortic insufficiency and other high output states the amplitude of pulsation in these disorders is consistent throughout the course of the vessel The presence of vigorous pulsations of the aortic arch therefore suggests the possibility of coarctation while the marked difference in the amplitude of pulsation in the pre and post obstructive portions of the vessel differentiates this lesion from other disorders associated with prominent arch pulsations

B Supravalvular Aortic Stenosis

Supravalvular aortic stenosis is a congenital obstructive deformity of the aorta which characteristically arises just distal to the coronary arteries and produces either localized or diffuse narrowing of the ascending aorta (19) Although the designation supravalvular stenosis encompasses a heterogeneous group of anatomic lesions three specific anatomic types have been described These include the membranous type consisting of a simple fibrous diaphragm containing a single perforation the hourglass type characterized by extreme thickening of the medial layer of the ascending aorta associated with an hourglass deformity of the external aspect of the vessel and corresponding narrowing of the aortic lumen and the hypoplastic variety characterized by uniform hypoplasia of the entire ascending aorta

In a recent study (18) we examined a group of 5 patients with supravalvular aortic stenosis (4 hourglass and 1 hypoplastic to evaluate the ability of cross sectional echocardiography to visualize the area of obstruction and to determine the severity and extent of the lesion In each of these cases there was a clearly defined area of decrease in aortic luminal diameter beginning superior to the distal margin of the sinuses of Valsalva and extending to involve a variable portion of the proximal ascending aorta Fig 4 is a characteristic recording from a patient with supravalvular aortic stenosis In this recording there is narrowing of the aortic lumen produced by an inward bending of the echoes from the anterior and posterior aortic walls at the junction of the superior border of the sinuses of Valsalva and the more distal ascending aorta The area of obstruction coin

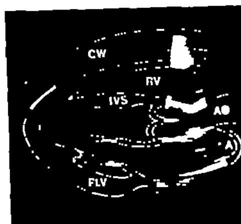


Fig 4: Cross-sectional echogram from a patient with moderately severe supravalvular aortic stenosis of the hourglass variety I this figure there is an area of aortic narrowing or constriction occurring at the level of the junction of the superior margi of the sinuses of Valsalva and proximal ascending aorta The obstruction is reflected by an inward curvature of the echoes from the anterior and posterior margins of the aortic walls which produces a restriction in lumina l diameter Distal to the area of bstruction there is a gradual increase in aortic diameter



Fig 5 Angiogram corresponding to the cross-sectional study in Fig 4 Again the area of marked decrease in aortic diameter at the superior margin of the sinuses of Valsalva is evident

cides spatially with the superior margin of the left atrium Distal to the area of obstruction the walls of the aorta gradually separate to return to a more normal luminal diameter Fig 5 is an angiogram of the ascending aorta from the same patient demonstrating the similarity in location and extent of the obstructing lesion

In order to determine the ability of the cross sectional echogram to accurately define the size of the aortic lumen at the level of obstruction the aortic diameter at the point of maximal narrowing determined from the cross sectional echogram was compared to the similar value measured from the angiogram In each of these cases the echocardiographic dimension was within 3 mm of the corresponding angiographic dimension In addition in 3 of the 4 patients with hourglass type lesions in whom the full extent of the area of obstruction could be recorded by the cross sectional technique the cross sectional estimate of extent of obstruction was within 5 mm of the correspon ding angiographic dimension In the single patient with hypoplasia of the ascending aorta the area of obstruction was felt to involve the entire vessel by both techniques

Finally due to the normal variability of the outflow diameter between the sinuses of Valsalva and proximal ascending aorta it may be difficult in the individual cases to differentiate normal change in diameter from mild supravalvular obstruction In order to examine this question the variabi lity in outflow tract dimension in a group of 20 normal subjects was compared with that observed in patients with supravalvular stenosis In each of the 20 normal patients the aortic diameter at the aortic annulus was equal to or slightly smaller than the corresponding diameter at the superior margin of the sinuses of Valsalva In none of these cases did the diameter decrease between these two levels In contrast in each of the 4 patients with hourglass type lesions the diameter decreased markedly from the aortic annulus to the proximal ascending aorta at the superior margin of the si nuses of Valsalva This decrease in diameter ranged from 25 to 61 % and in this small group appeared to correlate with the peak systolic gradient at the level of obstruction

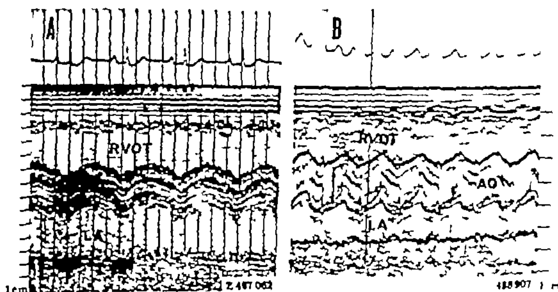


Fig 6 M-mode echocardiographic recording from two patients with valvular aortic stenosis Panel 6A shows a dense mass of linear echoes recorded from the aortic root with absence of apparent opening of the aortic valve suggesting severe stenosis At cardiac catheterization however the patient had a very mild valvular lesion In contrast Panel 6 B is a recording from a child with severe valvular aortic stenosis In this study th aortic leaflet separation and apparent valve opening appeared to be normal This figure illustrates the problems which occur in attempting to estimate the severity of aortic stenosis from the M-mode record RVOT-right ventricular outflow tract AO= aorta LA=left atrium

Although this is a preliminary study in a relatively small group of patients it does indicate that the cross sectional technique can accurately visuali ze the supravalvular area of the aorta detect obstruction in this region

determine the degree and morphologic characteristics of the obstructing lesion and by comparing the diameter at the level of obstruction to more normal areas of the outflow tract provide at least a rough estimate of the severity of the obstructing lesion

C. Valvular Aortic Stenosis

The M-mode echocardiogram has been widely used in an attempt to diagnose valvular aortic stenosis (12 13 14 20) In addition attempts have been made to determine the degree or severity of stenosis based on the density of echo production from the stenotic valve (12) or direct measurement of aortic leaflet separation as a reflection of orifice size (14) While each of these observations has proven helpful in individual cases it has not been possible to reliably or consistently estimate the severity of aortic stenosis using M-mode echocardiography Fig 6 is an example of the difficulties encountered in attempting to estimate severity of stenosis from the M-mode record Panel A is a recording from a patient with calcific aortic stenosis The dense echo production from the aortic root and absence of recordable leaflet separation suggests severe stenosis; however at cardiac catheterization this patient had only a mild lesion This failure to appropriately reflect the severity of the stenotic lesion occurs because the M-mode beam may strike only a localized area of the aortic root recording dense bands of echoes from a region of calcification while failing to visualize and eccentric area of normal leaflet motion Panel B is a recording from a child with severe congenital valvular aortic stenosis (peak systlic gradient 154 mm Hg) In this figure the aortic leaflets separate widely suggesting apparent normal leaflet motion Assessment of the presence and severity of the congenitally stenotic valve is an area where the M-mode technique has been notably unreliable (12 14) This occurs because the narrow M-mode beam transsects the base of the domed valve where the leaflets lie perpendicular to the path of the beam and hence present strong reflecting



Fig 7 Long axis cross-sectional echogram from a child with congenital valvular aortic stenosis This recording illustrates systolic doming of the anterior and posterior aortic cusps together with a marked decrease in aortic valve orifice size (vertical arrow) There is accentuation of the inner margins of the valve cusps at the orifice due to elongation of the echoes from this interface This apparent artifact is due to the strong reflecting interface at the blood tissue margin which helps to highlight the valve orifice

Finally due to the normal variability of the outflow diameter between the sinuses of Valsalva and proximal ascending aorta it may be difficult in the individual cases to differentiate normal change in diameter from mild supravalvular obstruction In order to examine this question the variability in outflow tract dimension in a group of 20 normal subjects was compared with that observed in patients with supravalvular stenosis In each of the 20 normal patients the aortic diameter at the aortic annulus was equal to or slightly smaller than the corresponding diameter at the superior margin of the sinuses of Valsalva In none of these cases did the diameter decrease between these two levels In contrast in each of the 4 patients with hourglass type lesions the diameter decreased markedly from the aortic annulus to the proximal ascending aorta at the superior margin of the sinuses of Valsalva This decrease in diameter ranged from 25 to 61 % and in this small group appeared to correlate with the peak systolic gradient at the level of obstruction

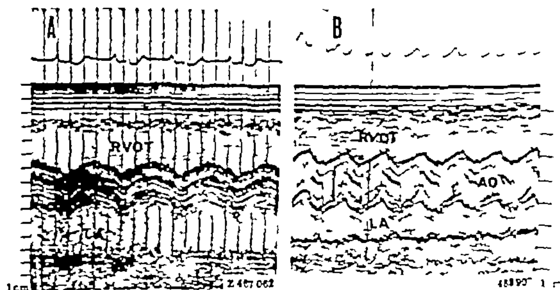


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maximum aortic cusp separations of 11 mm or less had been considered surgical candidates

Measurement of the maximum aortic cusp separation in the same group of patients using the M-mode system revealed several significant differences First in only 21 of the 28 patients (75%) was it possible to record an aortic valve orifice using the M-mode system Secondly in one patient with moderately severe non calcific aortic stenosis the M-mode markedly overestimated aortic valve orifice size while in three patients with mild aortic stenosis the M-mode record revealed aortic valve orifices of 10 mm or less suggesting a severe lesion Thus although it was possible to record the aortic valve orifice in the majority of patients using the M-mode technique in individual cases the derived data was clearly misleading

A follow up study (22) to determine the ability of this system to record the aortic valve in children revealed that in 93% of a group of 30 consecutive children the aortic valve could be recorded and the valve orifice visualized Because preliminary data suggested that correction of aortic valve orifice size for body surface area did not adequately relate aortic cusp separation to patient size a ratio was constructed between the maximum degree of cusp separation as a reflection of the actual aortic valve orifice and the aortic root diameter at the level of the aortic annulus as a reflection of potential orifice size Using this ratio a good correlation was demonstrated between both the peak systlic aortic valve gradient (Fig 9) and the aortic valve area calculated using the Gorlin formula These two studies suggest that cross sectional echography offers an improved method for the

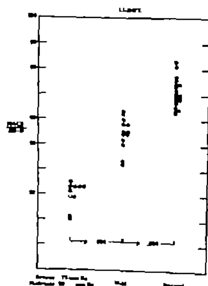


Fig 9: Diagram illustrating the relationship of maximum aortic cusp separation expressed as a percentage of the aortic root diameter to severity of aortic stenosis in a group of 25 children with valvular aortic stenosis and 22 normal subjects The left hand column contains children with moderate or severe valvular aortic stenosis (peak systolic aortic valve gradient >60 mm Hg) The middle column contains 13 children with mild valvular aortic stenosis (gradient<60 mm Hg) and the right hand column contains 22 normal patients (From Weyman AE et al Cross-sectional echocardiographic assessment of the severity of aortic stenosis in children Circulation 55 773 1977)

surfaces The apex of the dome where the leaflets lie parallel to the beam is poorly visualized and hence the flow limiting area and true degree of stenosis not appreciated

Cross-sectional echocardiography by expanding our field of vision and providing correct spatial orientation allows the entire aortic valve to be recorded simultaneously and hence its true shape and motion pattern appreciated (21 22) Fig 7 is a cross sectional echogram from a child with a congenitally stenotic aortic valve The cross-sectional system permits visulaization of the full spatial configuration of the domed valve as well as the obvious decrease in luminal diameter produced by the diminished valve orifice Comparing this recording with Panel B in Fig 6 emphasizes the relative merits of these systems Similarly in adults by sweeping the plane of the scan from the medial to the lateral surfaces of the aorta it is possible to visualize localized areas of normal leaflet motion and hence to more appropriately characterize the valve orifice in patients with densely fibrotic or calcific stenotic valves

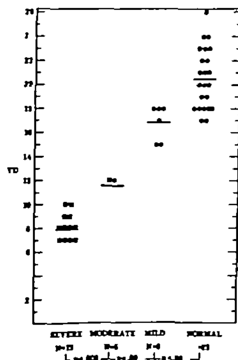


Fig 8 Relationship of maximum aortic cusp separation or aortic valve diameter (AVD) to severity of aortic stenosis in 28 adult patients with valvular stenosis and 25 normal subjects The squares in the figure indicate patients who were considered to be surgical candidates based on clinical and hemodynamic evaluation The circles indicate normal subjects and those patients not felt to require aortic valve surgery (From Weyman AE et al Cross-sectional echocardiography in assessing the severity of valvular aortic stenosis Circulation 52 838 1975)

In addition to detecting the presence of valvular aortic stenosis it is also possible by measuring the degree of aortic leaflet separation to estimate the severity of the stenotic lesion In an early study (21) of a group of 28 adult patients with calcific aortic stenosis it was demonstrated that a clear relationship existed between the maximum aortic cusp separation and the severity of stenosis (Fig 8) When this patient group was further examined to determine which patients were recommended for surgery based on clinical and hemodynamic criteria it was found that all patients with

left ventricular outflow tract in 16 patients with discrete subvalvular aortic stenosis and have observed two characteristic patterns of outflow obstruction which correspond to the subgroups noted above (24 25). In addition we have observed a single patient who appears to represent a third pattern of obstruction which differs markedly from either of the groups classically described In a group of three patients with obstruction produced by localized thin subvalvular membranes two discrete linear echoes were observed in the outflow tract proximal to the aortic valve These echoes appeared unattached to the anterior or posterior walls of the outflow tract and were felt to be produced by the blood tissue interface of the inner margins of the fibrous membrane Fig 10 illustrates the cross sectional appearance of this type of lesion The two characteristic linear echoes are present at the tip of the horizontal arrow In these cases there was some dynamic motion of these echoes towards each other during systole Fig 11 is a cross-sectional recording of a similar patient following surgical resection of the subvalvular membrane Although there is a small residual echo producing shelf along the posterior margin of the outflow tract the two linear echoes from the membrane itself are no longer present

In a second group of 12 patients whose subvalvular obstruction was characterized by a more diffuse area of outflow narrowing consistent with subvalvular fibromuscular rings or subvalvular tunnels a second pattern of outflow obstruction was observed This was characterized by an extensive area of inward bending of the linear echoes from the anterior and posterior wall of the outflow tract which produced an elongated area of outflow narrowing Fig 12 is an illustration of this type of obstruction The maximal area of narrowing is present at the tips of the vertical arrows

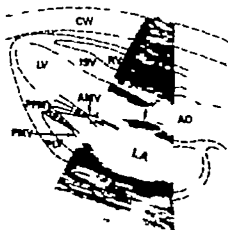


Fig 12 Long axis cross-sectional echogram from a patient with discrete subvalvular aortic stenosis produced by a more diffuse area of f bro-muscular narrowing of the outflow tract. The more generalized area of narrowing is characterized by extensive inward curving of the linear echoes from the walls of the outflow tract with resultant narrowing of the vascular lumen in this region. The area of maximal obstruction is indicated by the vertical arrows (From Weyman AE et al Localization of left ventricular outflow obstruction by cross-sectional echocardiography Amer J Med 60 33 1976)

detection of valvular aortic stenosis in patients with both calcific and congenitally stenotic aortic valves They further suggest that the cross sectional systems offer at least a semi quantitative method for determining the severity of stenosis

D Discrete Subvalvular Aortic Stenosis

Patients with discrete subvalvular aortic stenosis have conventionally been divided into two pathologic subgroups (23) In the first group the obstruction is produced by a thin discrete subvalvular membrane which may occur as an isolated lesion or may be superimposed on an area of fibromuscular narrowing of the outflow tract The second is characterized by a diffuse fibromuscular ring which constricts a more extensive portion of the subvalvular region This differentiation is clinically important since the extent of surgical revision and response to surgical repair differs markedly in these two groups of patients To date we have had the opportunity to examine the

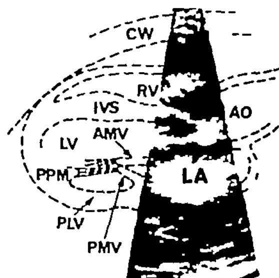


Fig 10 Long axis cross-sectional echogram from a child with discrete subvalvular aortic stenosis produced by a thin fibrous obstructing membrane located immediately beneath the aortic valve There are two linear echoes within the mid portion of the outflow tract produced by the blood tissue interface at the inner margins of the subvalvular membrane (horizontal arrow) The membrane itself which lies between these echoes and the walls of the vessel is oriented parallel to the interrogating beam and therefore not visualized. (From Weyman AE et al Localization of left ventricular outflow obstruction by cross-sectional echocardiography Amer J Med 60 33 1976)



Fig 11 Long axis cross-sectional echogram recorded post operatively from a child with type I (membranous) subvalvular obstruction The two linear echoes produced by the membrane are no longer present however there is a small residual echo producing ridge lying along the posterior margin of the outflow tract between the aortic root and anterior mitral leaflet The small area of residual narrowing is indicated by the vertical arrow (From Weyman AE et al Cross-sectional echocardiography in evaluating patients with discrete subaortic stenosis Amer J Cardiol 37 358 1976)

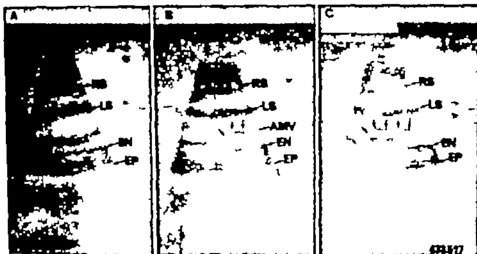


Fig 14: Serial long axis cross-sectional studies of the left ventricle at the level of the free edge of the mitral valve from a patient with IHSS Panel A is recorded 12 seconds after the R wave of the electrocardiogram and illustrates the normal systolic coaptation of the anterior and posterior mitral leaflets prior to the onset of systolic anterior motion. Panel B is recorded 8 04 seconds later illustrates the initiation of systolic anterior motion (vertical arrow) This systolic anterior motion begins at the point of coaptation of the anterior and posterior leaflets and spreads initially ex-periorly toward the interventricular septum In Panel C recorded two hundredths of a second later the sy tolic anterior motion has extended further anteriorly and distally toward the papillary muscles (vertical arrow) In the subsequent frame the leaflet has moved fully up against the interventricular septum and can no longer be clearly distinguished from the septal echoes

location of the systolic anterior motion relative to the closure point of the anterior mitral leaflet and the manner in which this obstruction develops Systolic anterior motion begins at the junction of the anterior and posterior mitral leaflets and spreads anteriorly toward the interventricular septum and distally toward the papillary muscles Henry et al (27) in a combined cross sectional and M-mode study showed a relationship between the distance of the anterior mitral leaflet from the interventricular septum and the occurrence of obstruction They further demonstrated that the abnormal anterior mitral leaflet motion occurred in the plane perpendicular to the pull of the papillary muscles suggesting that the papillary muscles did not draw the anterior leaflet up against the enlarged septum as had been previously suggested They concluded based on these observations that the phenomenon of systolic anterior motion or functional obstruction was produced by a Venturi effect caused by the acceleration of blood through the narrowed outflow space between the mitral leaflet and the interventricular septum and hypothesized that the creation of obstruction was dependent upon a critical distance between these two structures for any given rate of ejection Thus while the studies have to date not expanded

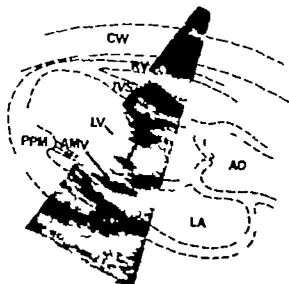


Fig 13 Long axis cross-sectional echogram of the left ventricular outflow tract from a patient with a variant of discrete subvalvular aortic stenosis In this patient there is a marked increase in septal thickness at the basal portion of the interventricular septum producing an area of shelf like narrowing of the outflow tract There is corresponding systolic anterior motion of the mid portion of the mitral valve The maximal area of obstruction is indicated by the vertical arrow (From Weyman AE et al Localization of outflow obstruction by cross-sectional echocardiography Amer J Med 60 33 1976)

The final type of outflow obstruction was observed to occur at a slightly lower level of the outflow tract In this case there was a localized area of marked increase in septal thickness occurring at the basal margin of the interventricular septum and producing an area of shelf like obstruction extending downward into the outflow tract There was a corresponding fixed echo extending anteriorly from the mid portion of the anterior mitral leaflet (fig 13) During systole there was dynamic anterior motion of this localized protrusion of the anterior mitral leaflet toward the downward projection from the interventricular septum The remainder of the septum was of normal thickness as was the posterior wall The septal posterior wall ratio at the level of the free edge of the mitral valve therefore was normal

E Idiopathic Hypertrophic Subaortic Stenosis

M-mode echocardiography ha been a sensitive method for diagnosing idiopatic hypertrophic suboartic stenosis (6 7) The resolution and sampling rate of this system permits the thickness of the interventricular septum to be accurately determined and the abnormal motion patterns of the anterior mitral leaflet clearly recorded In addition to permitting the diagnosis of IHSS the M mode system has allowed the underlying genetic marker asymmetric septal hypertrophy (ASH) to be defined (11 26) and the hereditary pattern of this lesion to be delineated (10) In addition some estimate of the severity of obstruction can be determined (8) While probably not significantly adding to our ability to diagnose IHSS the cross sectional system permits the location and nature of the obstructing lesion to be more clearly defined Several authors have examined the pattern of anterior mitral leaflet motion in patients with IHSS using different cross sectional systems and confirmed the location within the ventricle (27 28) and pattern of development of the obstructing lesion Fig 14 is a series of three recordings demonstrating the

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IHSS they do permit a relatively clear visualization of the pattern of obstruction and its development In this way the cross sectional system should help in understanding the patholophysiology of this phenomenon

CONCLUSION

As suggested in this report cross-sectional echocardiography is a valuable method for visualizing areas of obstruction at all levels in the left ventricular outflow tract It is particularly useful for defining regional changes in vascular size in a tubular structure such as the aorta By permitting visualization of the aorta both proximal and distal to the area of obstruction it allows the characteristic change in luminal diameter to be more fully appreciated At the valvular level the cross-sectional technique permits the full geometric configuration of the domed stenotic valve to be visualized thereby allowing the stenotic valve itself to be detected and the severity of the obstructing lesion estimated In areas of functional obstruction the cross sectional system allows the pattern of development of the obstruction to be more fully visualized and hence the pathophysiologic mechanisms producing this obstruction examined In addition to defining individual areas of outflow obstruction the ability to quickly examine the entire length of the left ventricular outflow tract should permit presence of multiple lesions to be detected The cross sectional technique should therefore be an important tool in the armamentarium of those interested in detecting and defining the morphologic and functional characteristics of lesions producing left ventricular outflow obstruction

ACKNOWLEDGEMENT

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THE USE OF M-MODE ECHOCARDIOGRAPHY IN ISCHAEMIC HEART DISEASE

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The characteristic feature of left ventricular involvement in ischaemic heart disease is its regional distribution due to the non-uniform nature of the coronary artery lesions This results in a number of disturbances of function of which the best recognized are a regional reduction in wall movement during systole aneurysm formation popularly supposed to be accompanied by para doxical movement and finally a generalized reduction in wall movement accompanied by an increase in cavity size so-called ischaemic cardiomyopathy These abnormalities all have in common a disturbance in the overall amplitude or direction of wall movement and their analysis in individual patients is usually based merely on inspection of angiograms Another type of interference with the action of the left ventricle may occur in ischaemic heart di sease however in which the overall amplitude and direction of wall move ment are both normal but in which its timing is disturbed This is much harder to characterize by direct inspection of the angiogram and yet may have effects on left ventricular function out of all proportion to the ex tent of myocardium involved by causing incoordinate contraction M-mode echo cardiography allows left ventricular endocardium to be unequivocally identified throughout the cardiac cycle and its movement recorded with a frequency response considerably superior to that of current angiographic techniques so that it is an excellent method for the analysis of these disturban ces

In figure 1 is shown the echocardiogram of a patient who developed a low output state after cardiac surgery It will be seen that though the ampli tude of septal movement is reduced as is frequently the case after open heart surgery that of posterior wall movement is normal However it is apparent from the mitral valve echo that virtually all the increase in transverse diameter that occurs does so before the onset of mitral valve opening and therefore before the onset of filling This increase in left ventricular dimension thus represents no more than a change in cavity shape during the period of isovolumic relaxation and as such likely to have contributed to poor overall left ventricular performance Wall movement in this

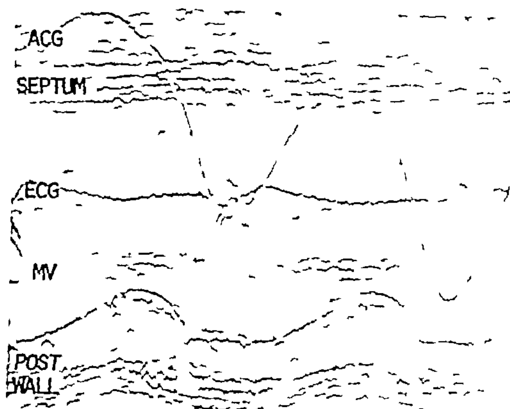


Fig 1 Echocardiogram showing left ventricular cavity and mitral valve echoes from a patient who developed a low cardiac output after surgery Mitral valve opening is delayed with respect to wall movement

patient is abnormal not in terms of its magnitude or direction but in its timing and it has been detected by considering the dimension not in isolation but by correlating it with events referable to the function of the cavity as a whole here the start of filling This method has proved a sen sitive one and abnormalities of isovolumic relaxation have been detected in patients with coronary artery disease where they correlate closely with the presence of regional reduction in wall movement seen on angiography (3)

The onset of mitral valve opening is only one of several ways in which the timing of overall left ventricular function can be assessed A more versa tile one is to use the left ventricular pressure trace to construct pressure-dimension loops The normal pressure-dimension loop is approximately rectangular (Fig 2) with little change in dimension during the upstroke and downstroke of the pressure trace which approximate in timing to the periods of isovolumic contraction and relaxation Conversely during ejec tion and filling changes in pressure are small The rectangular configura tion of the loop has functional significance in that the area of the loop represents the actual work done per unit area on the circulation by myocardium in the region studied while the maximum work that could have been done by the myocardium operating over the same range of pressure and

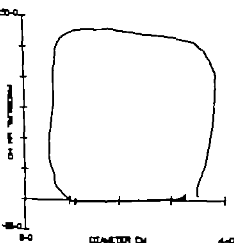


Fig 2 Pressure-dimension loop from a normal subject

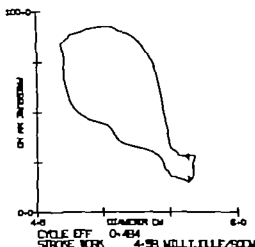


Fig 3 Pressure-dimension loop from a patient with ischaemic heart disease

dimension is given by the product of the two ie by the area of the rectangle that just encloses the loop The ratio of loop area to that of the rectangle thus represents the efficiency of transfer of mechanical energy generated by the myocardium to the circulation The pressure-dimension loop from a patient with ischaemic heart disease is shown in fig 3 It is apparent that the loop is distorted due mainly to dimension changes during the two isovolumic periods causing a drop in the efficiency of energy transfer to less than 60% Pressure-dimension loops can thus be used to demonstrate incoordinate contraction and when abnormalities of this sort occur during the isovolumic periods they may have considerable functional significance

Unfortunately measurement of left ventricular pressure requires cardiac catheterization In order to detect abnormal wall movement however it is not the absolute value of pressure that is required but only the timing of the upstroke and the downstroke and these latter have been shown to be very close to the corresponding events on the apexcardiogram (2 5) We have therefore explored the use of loops constructed from left ventricular dimension and apexcardiogram which have proved to be rectangular in all of more than 50 normal subjects studied In the presence of mitral regurgitation there is a reduction in dimension during the upstroke and of aortic regurgitation there is an increase in dimension during the downstroke as would be expected from the basic haemodynamic disturbances in these conditions many patients with ischaenic heart disease similar abnormali

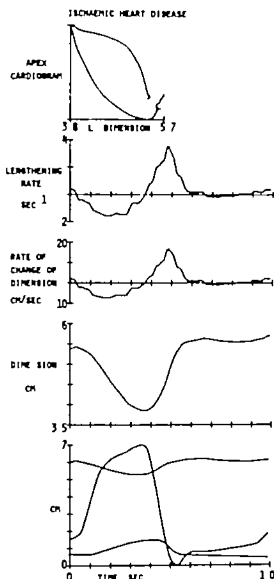


Fig 4 Apexcardiogram echo dimension loop from a patient with ischaemic heart disease There is a reduction in dimension during the upstroke and an increase in dimension during the downstroke of the apexcardiogram

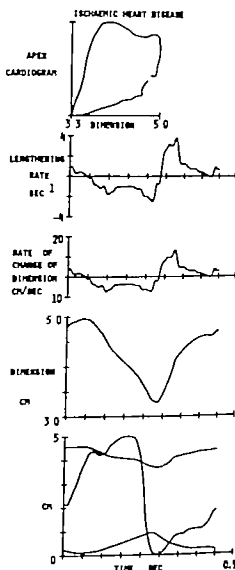


Fig 5 Apexcardiogram echo dimension loop from another patient with ischaemic heart disease The abnormalities are the reverse of those shown in fig 4

ties may also be found in the absence of valvular regurgitation examples being given in fig 4 and 5 In these circumstances a reduction in dimension during the upstroke of the apexcardiogram represents an abnormality of isovolumic contraction and during the downstroke one of early relaxation Such abnormalities can also be detected by suitable analysis of angiograms (3) (Prewitt and Brown 1976) Using these methods angiograms and apexcardiogram-echo dimension relations were compared in 50 patients with ischaemic heart disease In this study (Doran Traill Gibson and Brown unpublished) both specificity and sensitivity of the echo method were found to be greater

than 80 % with respect to the angiograms The method has also been of value in detecting incoordinate contraction in patients with valvular heart disease or cardiomyopathy in the absence of coronary artery disease It is useful in the follow-up of patients after saphenous by pass grafting when successful surgery may be followed by a return of the loop towards normal Finally it can detect postoperative left ventricular disease after valve replacement and thus monitor the quality of myocardial preservation (4)

This approach clearly does not replace left ventricular angiography and coronary arteriography as a means of studying patients with ischaemic heart disease However using traditional methods the nature of the complex physiological disturbance to left ventricular function may not be apparent from delineation of a series of anatomical abnormalities and it is in this field that the method appears to have value It is non-invasive so that repeated observations can be made in individual patients and it can be performed in circumstances such as the postoperative ward where cardiac catheterization would not be possible It is a simple way of detecting the presence of incoordinate contraction in patients with any type of heart disease and of following changes due to therapy or progression of underlying pathological processes

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EFFECT OF INCREASES IN AFTERLOAD ON THE SYSTOLIC THICKENING OF ACUTELY ISCHEMIC MYOCARDIUM

AN EXPERIMENTAL ECHOCARDIOGRAPHIC STUDY

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ABSTRACT

Changes in arterial blood pressure have been shown to alter epicardial ST segment elevations and have been advocated to minimize infarct size and salvage ischemic myocardium The effect of such changes on the regional function of ischemic myocardium has not been established To investigate this we studied the effect of increased afterload on the systolic wall thickening and myocardial perfusion of ischemic ventricular myocardium In 20 open-chest dogs an echocardiographic transducer was fixed to the exposed right ventricle and directed to record the motion of the left ventricular posterior wall Posterior ischemia was created by occlusion of the circumflex coronary so that the ultrasound beam registered the motion of acutely ischemic myocardium The ratio of end-systolic to end-diastolic posterior wall thickness (PTs/PTd) was greater than 1 (i e systolic thickening) before and less than 1 (systolic thinning) after posterior ischemia Mean arterial pressure was then increased by infusion of methoxamine (MX) or norepinephrine (NE) or by aortic constriction (CN) PTs/PTd improved from 0 89$\pm$ 0 03 to 1 10$\pm$ 0 06 ($p<0$ 05) with CN Perfusion of the ischemic areas assessed with 8μ radioactive labled microspheres showed a corresponding improvement; with MX ischemic myocardial perfusion improved from 32 4$\pm$6 2 to 59 6$\pm$13 8 ml/ 100g/min ($p<05$) and with CN perfusion rose from 30 2$\pm$9 3 to 43 8$\pm$10 3 ml/100g/min ($p<0$ 5) Thus increase in afterload improved both the perfusion and regional function of acutely ischemic myocardium

Changes of arterial blood pressure have been shown to alter epicardial ST segment elevations in dogs subjected to acute coronary occlusion Such changes may be useful in patients with acute myocardial infarction to "salvage jeopardized myocardium (1) The effect of such arterial pressure changes on the regional function of acutely ischemic myocardium has not been established

The purpose of this study was to assess the effect of increases in afterload on the function of acutely ischemic myocardium and to correlate the observed changes with regional myocardial perfusion We also wished to compare the effects of different methods of increasing afterload and therefore studied 3 agents norepinephrine a vasoconstrictor with positive inotropic effects and direct effects on coronary vessels; methoxamine a vasoconstrictor with beta adrenergic blocking properties which also has direct effects on coronary vessels and aortic constriction which has no direct inotrophic or coronary vasoactive effects An echocardiographic technique was used to measure dynamic changes in left ventricular wall thickness a recently emphasized parameter of regional myocardial function in the presence of ischemia (2)

METHODS

Twenty adult mongrel dogs weighing 16 to 23 kg were anaesthetized with chloralose-urethane IV An endotracheal tube was placed and the dogs were ventilated using Harvard respirator room air and supplemental oxygen Arterial pO_2 and pH were monitored frequently and were maintained in a physiologic range using adjustments of tidal volume Via a midsternal thoracotomy and pericardiotomy the heart was exposed and suspended in a pericardial sling The circumflex coronary artery or posterior descending coronary artery was dissected free and a snare ligature placed around it Heparin (250 units/kg IV) was given and ## 8 French polyurethane catheters were inserted retrograde into the left ventricle and aortic root for pressure monitoring using Statham P23 strain gauges at midchest level An electrocardiogram was also displayed Recordings were made utilizing an Electronics for-Medicine DR 12 multichannel photographic recorder

REGIONAL MYOCARDIAL FUNCTION

Echocardiographic recordings of the interventricular septum left ventricular

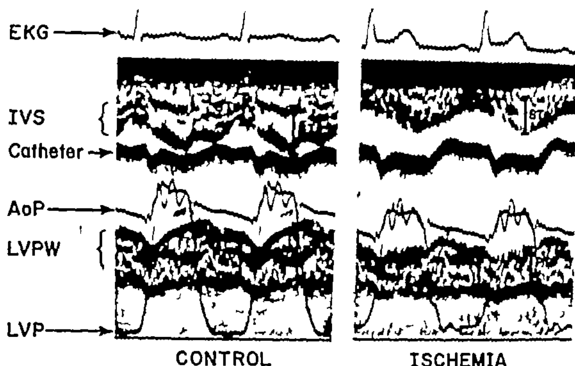


Fig 1 Illustrative echocardiographic recordings before ("control") and 20 minutes after ("ischemia") posterior coronary occlusion The vertical bars indicate end-diastolic and end-systolic septal and posterior wall thickness End-systolic septal thickness was taken at the point at which the septum was thickest With posterior ischemia abolition of normal posterior wall thickening occurred while septal thickening was preserved Abbreviations EKG = electrocardiogram IVS = interventricular septum AoP = aortic pressure LVPW = left ventricular posterior wall LVP = left ventricular pressure STd = septal thickness end-diastolic STs = septal thickness end-systolic PTd = posterior wall thickness end-diastolic PTs = posterior wall thickness end-systolic

cavity and left ventricular posterior wall were obtained using a method which has previosly been described in detail (3) Briefly a 2 25 mHz 5 cm focussed transducer was placed on the exposed anterior right ventricular surface and directed inferiorly to the mitral leaflet echoes to record the left ventricular posterior wall motion Thus after circumflex coronary occlusion the ultrasound beam was reflected from and registered the motion of acutely ischemic posterior myocardium (4 5) The transducer was fixed to a rigid bar to minimize transmitted motion from the heart and to provide a fixed reference point

To verify structure identification we injected 5 ml of normal saline through a catheter in the left atrium this produces ultrasonic contrast reflections which fill the chamber and outline the endocardial-blood interfaces (6) The sensitivity of the ultrasonoscope was manipulated to best define the epicardial and endocardial echoes The thickness of the septum and posterior wall was measured at end-diastole and end ...ole

The exact points of measurement are shown in Fig 1 The ratio of end systolic septal thickness (STs) to end-diastolic septal thickness (STd) was expressed as a simple ratio (STs/STd) A similar expression was used for the posterior wall thickness (PTs/PTd)

MYOCARDIAL PERFUSION

Left ventricular myocardial perfusion was determined using 7 10 μ micro spheres labeled with ^{141}Ce ^{85}Sr ^{51}Cr and ^{46}Sc For each perfusion measu rement the vial containing the microspheres and one drip of Tween-80 was agitated mechanically for at least 3 minutes to achieve adequate disper sal of the spheres The microspheres were suspended in saline and injected over a 5 second period into the left atrium left atrial catheter was then flushed with 5 ml of saline Beginning one minute before injection and continuing for 3 minutes after injection blood for reference flow determi nations was withdrawn from the right brachial and femoral arteries simulta neously at 2 06ml/min

After the echocardiographic recordings were completed two metal probes were positioned along the ultrasound transducer and passed through the heart in parallel to mark the path of the ultrasound beam To minimize deformation of the left ventricular wall (and consequent errors in beam localization) we placed sharp #20 needles through the beating heart The points of in- tersection of the probes with the left ventricular posterior endocardium were noted to verify that the specific myocardial segments traversed by the ultrasound beam were hypoperfused segments from the area supplied by the ligated coronary artery The animals were then killed with an injection of potassium chloride

The heart was excised and the free walls of the right ventricle the right and left atrium great vessels valves surface vessels and epicardial fat were removed Utilizing the posterior descending coronary as a reference point, the left ventricle was divided into four equal levels of eight seg ments each and each segment was divided into three layers endocardium mid-wall and epicardium Thus the left ventricle was divided into 96 seg ments of about 1 6x1 6x0 3 cm in size with an average weight of 0 8 g The relative geometric position of each segment was constant from animal to animal

Using techniques previously described in detail (7) we determined the per fusion of each of the 96 small myocardial segments as well as the size of the ischemic area and the endocardium-epicardium perfusion ratio Ischemic

segments were identified utilizing a statistical method (7) which in ef fect estimates the heterogeneity of perfusion to normally perfused seg ments and then uses this information to establish the level below which perfusion of normal segments does not fall Segments found to have such abnormally low perfusion (seen only following coronary ligation) were classified as ischemic

EXPERIMENTAL PROTOCOL

Prior the coronary occlusion control hemodynamic and echocardiographic recordings were obtained and an injection of microspheres made The previouslyplaced circumflex or posterior descending ligature was then tightened to occlude the artery The animals were allowed to stabilize for 20 mi nutes after which a second set of hemodynamic and echocardiographic recordings were made and another injection of microspheres with a different label was made Hereafter the animals were divided into three groups Group I animals (n = 7) received norepinephrine 0 7 to 15 0 µg/min IV in order to raise mean aortic pressure to approximately 120 % and then 140 % of the the level at the initial postcoronary occlusion recording Group II animals (n = 8) received methoxamine 0 10 to 1 2 mg/min IV to similar end points In group III dogs (n = 5) an umbilical tape was placed around the descending aorta and this was tightened to two different levels of aortic constriction In each case the increase in pressure was maintained for at least 5 minutes while echocardiographic and hemodynamic recordings were obtained microspheres injected and reference blood withdrawal accomplished Standard statistical methods were used for analysis All data are expressed as mean±standard error of the mean

RESULTS

Hemodynamic data The hemodynamic data are summarized in table 1 The control mean aortic pressures were higher in the group of dogs which were to receive methoxamine after coronary occlusion The reason for this is not clear Despite our attempts to achieve comparable end points methoxamine also effected a greater relative rise in mean aortic pressure than did norepinephrine Aortic constriction produced a smaller rise in aortic mean pres sure than did the two drugs since this intervention produced primarily sys tolic hypertension with a relatively modest rise in diastolic pressure

Myocardial function The echocardiographic wall thickening data are summa rized in tabl 1 and in fig 2 3 4 The radio PTs/PTd was 1 0 or greater (i e systolic thickening) in all of the 20 control recordings and less

Table 1

A. Animals receiving methoxamine after coronary occlusion (n=[illegible])

	Control Mean±SEM	Coronary Occlusion Mean±SEM	Intervention 1st level Mean±SEM	Intervention 2nd level Mean±SEM
Heart rate, beats/min	140±6	129±9*	128±8	124±7
Aortic systolic pressure, mmHg	144+10	124±10	157±11	183±13*
Aortic mean pressure, mmHg	130+10	110±11	143±11	174+14*
Aortic diastolic pressure, mmHg	123+10	104±11	136±11	165+14*
LV end-diastolic pressure, mmHg	8+4	14+1	14±2	19±3
PTs/PTd	1 14+0.07	0.90±0.03	1.03±0.04	1 10±0.04*
STs/STd	1.30±0.07	1.37±0.13	1.27±0.06	1.24±0.07
Perfusion, ischemic segments ml/100g/min	87.2±11.8	32.4±9.2	46.9±11.3	80 6+13.0*
Endo-Epi ratio, ischemic segments	1.2+0.1	0.7±0.1	0.6±0.2	0.8±0.1
Perfusion, nonischemic segments ml/100g/min	86.9±11.3	73.7±10.8	77.4+10.6	103.9±11 9*
Endo-Epi ratio, nonischemic segments	1.2±0.1	1.2±0.0	1.2+0.1	1.2±0.1

B. Animals receiving norepinephrine after coronary occlusion (n=7)

	Control Mean±SEM	Coronary Occlusion Mean±SEM	Intervention 1st level Mean±SEM	Intervention 2nd level Mean±SEM
Heart rate, beats/min	140±9	131±9	135±4	148±5*
Aortic systolic pressure, mmHg	108+4	97±4	118±6*	144±5*
Aortic mean pressure, mmHg	90±4	85+4	103±5*	130±5*
Aortic diastolic pressure, mmHg	80+4	73±4	89±4*	113±5
LV end-diastolic pressure, mmHg	12±4	15+3	15±3	16±5
PTs/PTd	1.10±0.06	0.86±0.03	0.90+0.03*	0.97±0.03*
STs/STd	1.15±0.07	1.43±0 10	1.29±0.08*	1.34±0.07
Perfusion, ischemic segments ml/100g/min	70.9+4.6	33.1±4.6*	31 9±5.8*	47 1±9.2*
Endo-Epi ratio, ischemic segments	1 1±0.1	0.7±0.1	0.7+0 1	0.7±1.0
Perfusion, nonischemic segments	71.6±7 1	70.8±9.5	88.2±11 4	118.1±9.0*
Endo-Epi ratio, nonischemic segments	1.0+0.1	1 1+0.0	1 1+0.0	1 1±0.1

C. Animals undergoing aortic constriction after coronary occlusion (n=5)

	Control Mean±SEM	Coronary Occlusion Mean±SEM	Intervention 1st level Mean±SEM	Intervention 2nd level Mean±SEM
Heart rate, beats/min	170±12	170±11	174±11	178±14
Aortic systolic pressure, mmHg	119+12	118±15	138±10*	167±10*
Aortic mean pressure, mmHg	104+13	100±15	118+10*	139±12*
Aortic diastolic pressure, mmHg	97±13	95+15	106±17	109±11
LV end-diastolic pressure, mmHg	13±3	11±2	14±4	23±7*
PTs/PTd	1.23±0.06	0.85±0.03	0.97±0.04*	0.94±0.03
STs/STd	1.36±0.10	1.30±0 13	1 19±0.08	1.27+0.06
Perfusion, ischemic segments ml/100g/min	80.3±13.1	38.2±9.3	28.3±7.2	43.8+10.3*
Endo-Epi ratio, ischemic segments	1 1+0.0	0.8±0.2	0.8+0.2	0.8±0.2
Perfusion, nonischemic segments ml/100g/min	84.5+11.4	86.1±15.8	81 4+12.2	133.0±20.3*
Endo-Epi ratio, nonischemic segments	1 1+0.0	1 1±0.0	1.0+0.1	1.5+0.4

Abbreviations: *p<.05 control vs coronary occlusion
*p<.05 intervention vs. coronary occlusion
LV left ventricle. Endo-Epi endocardial-epicardial For PTs/PTd and STs/STd see text.

than 1 (systolic thinning) in 17 of the 20 dogs after posterior ischemia (In the three remaining animals the ratio fell to 1 0) Mean PTs/PTd increased with methoxamine (Fig 2) with norepinephrine (Fig 3) and with aortic constriction (Fig 4) Considering the effects of these maneuvers on nonischemic myocardium (the interventricular septum) STs/STd of all the dogs exceeded 1 0 control (i e systolic septal thickening) After posterior coronary occlusion STs/STd of the whole group increased from 1 27+0 04 to 1 37+0 07 (p=NS) With each subsequent intervention STs/STd fell slightly but never to 1 1 0

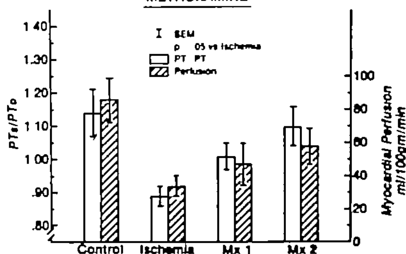


Fig 2 Effect of methoxamine on ischemic posterior wall thickening and perfusion SEM = standard error of the mean MX = methoxamine

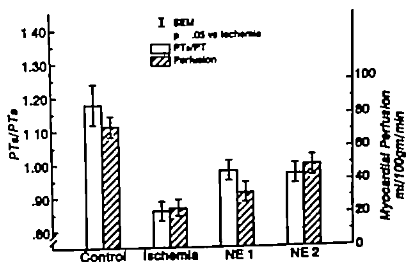


Fig 3 Effect of norepinephrine on ischemic posterior wall thickening and perfusion NE = norepinephrine

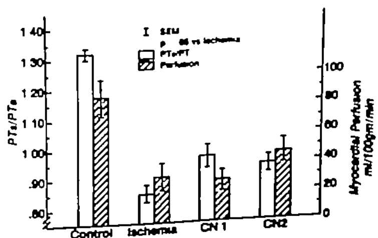


Fig 4 Effect of aortic constriction on ischemic posterior wall thickening and perfusion CN = aortic constriction

Myocardial Perfusion The microsphere derived perfusion data are summarized in Table 1 and Fig 2 3 4 With methoxamine perfusion of the ischemic areas improved from 32 4 $\pm$ 6 2 to a maximum of 59 6 $\pm$ 13 8 ml/100 g/min ($p < 0$ 05) (Fig 2) With norepinephrine perfusion increased from 23 1 $\pm$ 4 6 to 47 1 $\pm$ 6 2 ml/100 g/min ($p < 0$ 05) (Fig 3) With aortic constriction the perfusion increased from 30 2 $\pm$ 5 3 to 43 8 $\pm$ 10 3 ml/100 g/min ($p <$ 05) (Fig 4) Perfusion of the nonischemic areas rose (Table 1) with each intervention The endocardial-epicardial perfu sion ratios were greater than one in control determinations and less than one in the ischemic areas after coronary occlusion With the interventions the en do-epi ratios did not change significiantly (Table 1)

DISCUSSION

In this study we used systolic thickening or thinning assessed echocardio-graphically to assess the function of acutely ischemic myocardium PTs/PTd appears to be influenced strongly by the perfusion of the area of myocardium sampled by the ultrasound beam since wall thickening was seen in normally perfused areas and wall thinning was associated with the severe hypoperfu-sion of the ischemic areas

Increases in afterload accomplished with any of the three interventions we used had beneficial effects on the thinning of acutely ischemic myocardium Thinning was virtually abolished with norepinephrine and aortic constriction (PTs/PTd approached 1 0) and with methoxamine thickening of the initially ischemic wall occurred These changes probably reflected improvement in the perfusion of the areas supplied by the occluded coronary artery; although perfusion of these areas was not restored to pre-occlusion levels signifi cant increases in perfusion did occur with each intervention Norepinephrine has positive inotropic effects and the improvement in PTs/PTd could be due to these However similar improvement occurred with methoxamine and aortic constriction which lack positive inotropic effects This again suggests that the change in thickening was primarily due to improved perfusion The rea son for the increase in flow to the ischemic areas is not determined by this study It may be due to increased collateral flow Or since the per-fusion distribution after coronary occlusion is spatially and temporarily heterogeneous it may primarily reflect improved perfosion to normally perfu-sed areas lying within the ischemic zone A mixture of both these mecha nisms is also possible

Perfusion of the nonischemic areas also rose with the pressor interventions but unlike the ischemic posterior wall this was accompanied by small declines

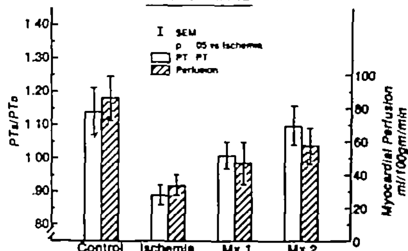


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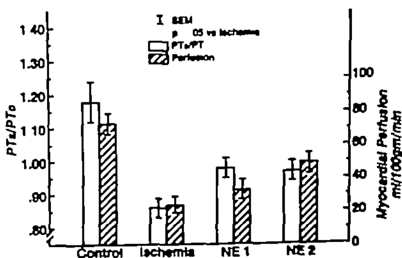


Fig 3 Effect of norepinephrine on ischemic posterior wall thickening and perfusion NE = norepinephrine

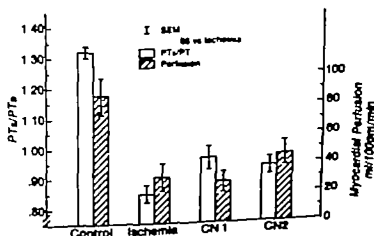


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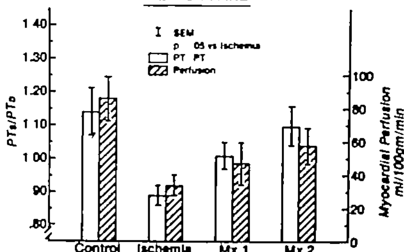


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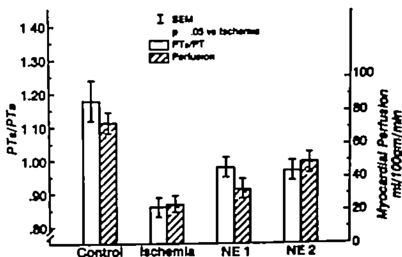


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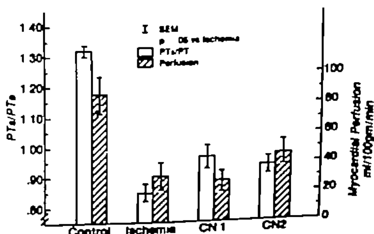


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11 CORYA, B C RASMUSSEN S , FEIGENBAUM H KNOEBEL S B and BLACK M J Systolic thickening and thinning of the septum and posterior wall in patients with coronary artery disease congestive cardiomyopathy and atrial septal defect. Circulation 55 109 1977

in the thickening of the nonischemic septum (STs/STd) Thus in nonischemic myocardium perfusion alterations within a physiologic range are probably not a major determinant of myocardial function

These results are compatible with other experimental studies Elevation of coronary perfusion pressure has been shown to reduce the extent of myocardial *damage after coronary occlusion in dogs (8 9) Hillis and Braunwald (1) sug*gest that this is because the deleterious effects of increased afterload on myocardial oxygen requirements are over-ridden by increases in collateral inflow to the ischemic area the rich collateral network in dogs fosters this Wyatt et al (10) showed that elevating arterial pressure with angiotensin produced an increase in coronary flow across an area of severe coronary stenoses and this caused lactate production to shift to extraction Systolic myocardial thinning probably will be useful to detect ischemia in patients As noted we found it to occur in severely hypoperfused areas in the animal Corya et al (11) showed in humans that systolic thinning occurred only in regions of myocardial ischemia or fibrosis In conditions such as atrial septal defect abnormalities of ventricular endocardial motion occurred but systolic thickening was preserved

Our observations on the effect of increasing afterload must be applied with caution to patients We assessed only the acute effects of the interventions their long term effects may not necessarily be similar The coronary collateral network in humans is less extensive than the dog and an increase in afterload in that situation may conceivably increase myocardial oxygen requirements out of proportion to the improvement in regional perfusion The initial level of systolic pressure and the presence of left ventricular failure may also affect the response to afterload manipulations in patients

ACKNOWLEDGEMENT

The authors gratefully acknowledge the technical assistance of Margaret Schrader Gil Koenigsaecker and Oscar Lim

This work was supported by NIH Grant #HL014388 and RCDA #HL00328

This paper reviews the reliability of the echoventriculographic method by comparing it with cineangiographic and autopsy findings Its clinical uses in the coronary care unit are outlined

PATIENTS

The accuracy of the echoventriculographic method in detecting regional asynergy of the left ventricle was studied in 112 patiens with acute or healed myocardial infarction Correlations were made with electrocardiography in 70 patients cineventriculography in 42 patients and with autopsy from 17 patients The normal series comparised of 42 healthy subjects (9)

THE ECHOVENTRICULOGRAPHIC SCANNING TECHNIQUE

The most important matter in assessing the myocardial infarction by ultrasound is to determine the ultrasonic scanning sites in relation to the established anatomical landmarks of the left ventricle First the beam direction is searched in which both the anterior and posterior mitral valve leaflets are recorded simultaneously (11) This basic beam direction is quite strictly defined in relation to the left ventricular anatomy Above this beam direction the aortic root is used as a second fixed orientating point at the level of the mitral valve annulus The apex is easy to find and serves as the most inferior scanning landmark in the vertical direction

In the horizontal plane the reference points are the anterior junction of the right ventricular wall and the septum the anterolateral and posteromedial edges of the mitral valve and the respective papillary muscles The anterior wall motion is scanned at several levels by directing the transducer from the aortic root or mitral valve level towards the apex and from the septal regions over the anterior right ventricular junction laterally The posterior wall is scanned at the upper and lower levels in relation to the mitral valve medially and laterally from the papillary muscle A standardized method was developed to record 4 anterior and 4 posterior wall locations from 4 standard precordial positions (9 11) Several additional positions are available according to the left ventricular enlargement

At each precordial position the probe is aimed as perpendicular as possible to the underlying left ventricular endocardial surface (11) This is based on observing a parallel motion of echoes from different myocardial layers both in the A-mode and M-mode display The upper septal and posterolateral walls are scanned from a precordial scanning position and axis (Fig 1) (9)

ACCURACY AND USEFULNESS OF ECHOVENTRICULOGRAPHY IN ACUTE MYOCARDIAL INFARCTION

M S NIEMINEN AND J HEIKKILÄ

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SUMMARY:

Echoventriculography is a noninvasive and three-dimensional ultrasonic technique capable to assess in detail the regional performance of the left ventricle Therefore the mechanical performance of the left ventricle after myocardial infarction is informatively assessed by the composite contributions made by infarcted and noninfarcted segments Its reliability has been confirmed by direct cineangiographic and autopsy correlations In clinical decision making such direct information is of great value both for diagnosis and therapeutic selection In the coronary care unit echoventriculography provides most information obtained by the less feasible invasive cineangiographic examinations

INTRODUCTION

Echocardiography has become an important method of investigation in cardiology Little information is available however on its use in patients with ischemic heart disease Abnormalities of the segmental wall motions of the left ventricle are most common in these patients (4) A multidirectional single probe technique has been developed in our laboratory for detailed study of these regional wall motions This scanning procedure, echoventriculography describes the left ventricular performance by a composite picture made up from sequential studies of wall motions of the multiple ventricular segments The method is capable of encompassing practically the entire left ventricle Its success is based on the use of multiple precordial transducer sites and directions and on careful adjustment of gain and reject sets (11 12)

Echoventriculography has proved to be useful and accurate technique for detection of the site and size of myocardial infarction Function of the noninfarcted regions of the left ventricle is assessed at the same time

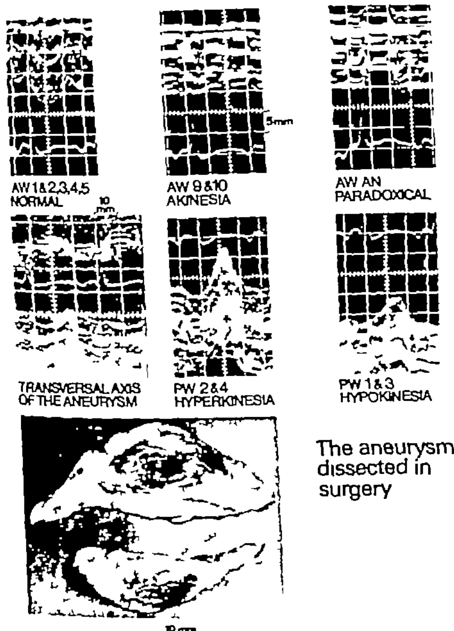
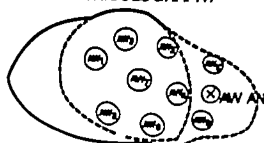


Fig 1

Even more lateral areas are feasible in those cases where the left ventricle is enlarged into the lateral direction (9 11) (Fig 1 AW AN and AW8 to A14 in Fig 5 in ref 12) It is particularly rewarding to record these sites to ...ysms following large anterior or anterolateral infarction



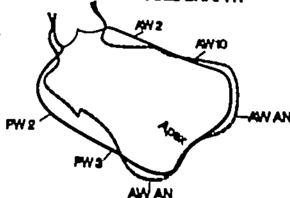


Fig 1 In a postinfarction aneurysm the location of the different types of regional wall motion abnormalities recorded by echoventriculography and cineangiography are in good agreement with each other and with QS-complexes of the anterolateral electrocardiographic leads as well as the aneurysm sac dissected at surgery The paradoxical bulging of the wall (AW AN) and the transversal axis (AN) of one of the two aneurysm sacs is shown measured from a point between location AW 9 and AW 10 Note the heavier M-mode lines of the stronger fibrous tissue echoes

This position is achieved when the transducer is moved from the mitral valve recording position to the left edge of the sternum and direced inferiorly and posterolaterally Position 2 is situated about 2 cm lateral to the mitral valve recording point now the beam traverses both the free anterior and free posterior wall segments at the upper half of the left ventricle (locations AW2 and PW2 Fig 1) Position 3 of the probe is one intercostal space below position 1 It is used to study the low septal and the inferolateral walls of the left ventricle (locations AW3 and PW3 Fig 1) The low free anterior and inferoposterior locations (AW4 and PW4 Fig 1) are correspondingly scanned from position 4 (9) These standardized scanning locations are required to obtain reliable data in the repeated studies

Additional positions are used for even more detailed estimation of the abnormalities of the left ventricular anterior wall motion High anterior (AW5) apical (AW6) and midanteroseptal (AW7) sites are scanned from the respective positions on the chest wall (Fig 1)

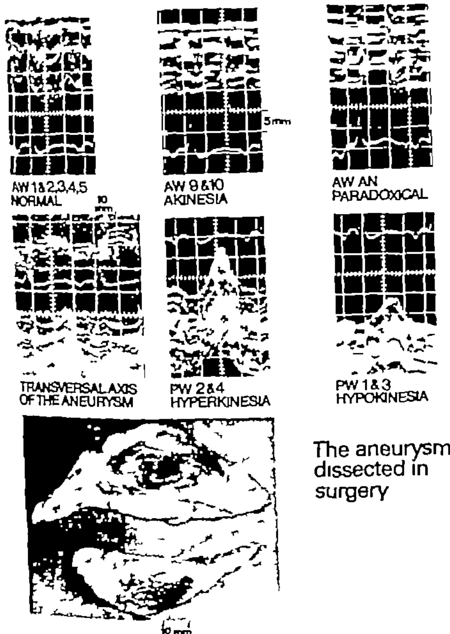


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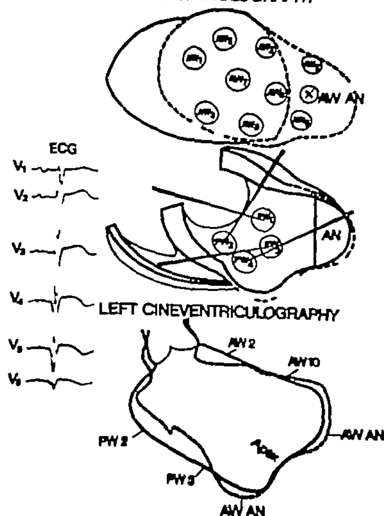


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LATERAL NONTRANSMURAL INFARCTION IN ECHO

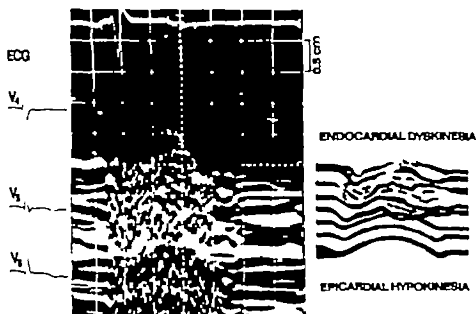


Fig 1. In acute subendocardial infarction the endocardial echo lines show dyskinetic motion while the epicardial layers contract in parallel way The total motion is usually hypokinetic the degree of which depends on the depth and severity of ischemia. Note the light echoes on the endocardial side with broken continuity during systole

In contrast the old lesion reflects the echoes in a uniform manner where the echolines move in parallel (Fig 1) during systole The echoes reflected from scars are much stronger than those of normal myocardium and their motion is hypokinetic akinetic or paradoxical depending on the depth of the lesion (Fig 1)

RELIABILITY OF ECHOVENTRICULOGRAPHY IN ESTIMATION OF THE MYOCARDIAL INFARCTION

REPRODUCIBILITY OF REPEATED MEASUREMENTS

The reproducibility of the sequential measurements is achieved by strict standardization of probe directions relative of the anterior and posterior mitral valve leaflets and other anatomical reference sites mentioned The accuracy in recording of the segmental wall motion is dependent on perpendicular directioning of the beam controlled by the parallel motion of myocardial echolines When in repeated studies the patient is lying in exactly the same position, the standardized technique allows accurate and reproducible recordings The axial resolution is theoretically less than 1 mm and in repeated studies the reproducibility of wall motion amplitude remained within 1 mm (9 11 12)

The sites at the posterior wall are usually scanned first the same gain and reject levels being employed for all sites A-mode echoes received from the posterior wall are positioned on the oscilloscope screen Fine adjustments are then made while the probe is moved slightly The echo patterns and necessary correlations are best observed in the A-mode display The probe is carefully rotated so that optimal endocardial epicardial and myocardial echoes are obtained with as few distortions as possible The motion-mode scannings are then recorded repeatedly on the memory scope and scannings of good quality are photographed with a Polaroid camera The anterior wall locations are recorded similarly but with a lower decibel gain value The amplitude of the regional wall motion mean systolic velocity and end systoli and diastolic wall thicknesses are measured (9) A quantitative echoventricul graphic contraction index was developed for the left ventricular performance by summing up the individual regional wall amplitudes The index is obtained from the sum of the amplitudes of the 7 (12) or 8 (13) standard sites (PW1-4 and AW1-4 Fig 1) the sum is then normalized by dividing it by the sum of corresponding mean normal amplitudes (9)

Echoventriculography detects myocardial ischemia or infarction by the loss of contractile function at that segment (4 17) On the basis of the normal values obtained from 42 healthy subjects (9) the following criteria for asynergic wall motions are defined Wall motion is termed hyperkinetic when its systolic amplitude is over 6 mm at the anterior wall and over 10 mm at the posterior wall These values exceed the mean normal anterior and posterior segment amplitudes of 4 5 mm and 8 5 mm by 1 standard deviation In hypokinesia the amplitudes are below 3 mm at the anterior and below 6 mm at the posterior wall segments being less than normal minus 1 standard deviation An akinetic wall shows negligible motion while in paradoxically moving segments the wall motion is outward instead of the normal inward during the greater part of systole (10) Nor does any systolic thickening of an akinetic or paradoxically moving segment take place This is a useful sign when the physiological asynergy at the septal regions often present in well trained subjects must be excluded

DIFFERENTIATION BETWEEN AN OLD SCAR AND A RECENT INFARCTION

An old myocardial scar is a much stronger reflector of ultrasound than is myocardial necrosis A recently ischemic tissue is edematous it shows a broken continuity of the M-mode echolines in systole (Fig 2)

The major practical advantage of echo in the regional wall motion analysis compared to regional hemiaxis shortening percentages by cine is that it directly provides the contraction amplitudes in absolute values These absolute motions however must be related to the size of the left ventricular cavity (13) On basis of these cineangiographic correlations echoventriculography seems to be a reliable and sensitive method for the assessment of left ventricular function noninvasively (10) This index is applicable with contraction abnormalities

CORRELATION WITH AUTOPSY FINDINGS

Echoventriculography was available in 17 patients with fatal myocardial infarction and of 2 more patients operated on for left ventricular aneurysm The direct measurements at autopsy or at surgery confirmed that the site of the myocardial infarction may be determined very accurately by echoventriculography during life The borders encompassing the infarcted myocardium was assessed by echo to fall into 7 sectors around the left ventricle At autopsy variation over the predetermined sector was exceptional and usually the echo border was within 1 cm of that actually noted at autopsy The same accuracy was achieved in the vertical direction on the size of infarct (H M to be published) Furthermore the capacity of ultrasound to differentiate old scars from fresh infarctions was confirmed by the pathological anatomical study Old fibrous scars were dissected by echo from recent damage in every case As yet this has not been possible with any other technique during life

USEFULNESS OF ECHOVENTRICULOGRAPHY IN ACUTE MYOCARDIAL INFARCTION

REGIONAL MYOCARDIAL INFARCTION

Earlier the technical difficulties inhibited echoventriculographic studies of the anterior myocardial wall motion With technical development of equipment and careful attention during the procedure the present method was successful in every patient in recording wall motions of the multiple posterior septal anterior and lateral left ventricular segments Attention has been recently paid by other investigators also to recording of multiple segments of the left ventricle Corya et al reported a success rate of 83% with a somewhat simpler recording technique (1) The present echoventriculographic method scans multiple segments around the entire left ventricle It provides a means to assess the

CORRELATION WITH ELECTROCARDIOGRAPHY

Echoventriculography and electrocardiography have agreed in every case on the anterior or posterior site of the acute myocardial infarction We have reported these relationships in detail earlier (4) and now the same good correlation is available in 70 patients In anterior infarctions the relationship was good also quantitatively The more precordial leads showed infarction pattern the more asynergic segments were noted in echo (4) (Fig 1) The estimation of the size of inferoposterior infarction by electrocardiography was less accurate with the few depicting leads available than by the echo scanning Echo also demonstrated the inferoposterior lesion to often extend into a posterolateral direction when ECG showed inferior damage only This slight difference is similar to that found in correlation of electrocardiograms with the autopsy data (7)

CORRELATION WITH CINEANGIOGRAPHY

Echoventriculography was compared with cineangiographic study of left ventricular function in 42 patients They had coronary artery disease ahd were studied for bypass surgery (10) Abnormal regional contraction was noted in 33 of the 42 patients by single plane cineangiography performed in the rightanterior oblique projection Any asynergic contraction noted in angiography was always correctly detected by echo Segments contracting normally in echo did so also in cine Besides this qualitative accuracy the degree of asynergic motion agreed with both methods (10) Echo was further able to scan left ventricular dysfunction in all these patients in those regions that do not become visualized in the single plane cine Hyperkinesia of the uninvolved areas was more readily detected by echo than by cine (30 vs 14 patients)

Cineangiographic and echoventriculographic contraction indices were developed for quantitative purposes (10) The overall correlation between them in the whole series was significant (r=0 62 P<0 005) The main reason for the weakening of the correlation was found to be the presence of either large apical asynergy or apical hyperkinesia Those cases excluded the correlation between the cine and echo contraction indices was very good (r = 0 91 p < 0 05)

The reliability of ejection fraction measurement by echo from the standard minor axis was not found to be good in the asynergic ventricles in relation to ejection fraction by area length method from cineangiography (r=0 38) (10)

severe infarctions from those with severe power failure or fatal course (r 0.79 p < 0.001) (14). In uncomplicated infarctions it was 78 $\pm$ 12 % of the normal with moderate left heart failure 55 $\pm$ 14 % while in severe power failure being only 35 $\pm$ 14 % (8). This index brings out clearly the team work of the infarcted and the noninfarcted ventricular segments. When the healthy segments contract vigorously the index is higher and the prognosis usually good. The larger the paradoxical area, the poorer the contraction of the noninfarcted myocardium, the lower is the index (14). This contraction index summed from the multiple ventricular sites also correlated with the echoventriculographic ejection fraction (r 0.60 p < 0.005).

IMPLICATION OF THE NONINFARCTED MYOCARDIUM

The function of the healthy myocardium was hypercontractile in 12 of the 30 patients (40%) but this occurred only in the uncomplicated (+27 % over normal) and moderately severe infarctions (+4%) (13).

The 4 patients who died in the group of 10 with pump failure had a very poor regional contraction index. It remained below 50% in all of them whose ejection fractions were below 30%. Remarkably, hyperkinesia was not detected at any noninfarcted site in the 10 patients with pump failure (14). The failure of the uninvolved myocardium to develop even a normal response obviously contributed to power failure in these patients; the mean conctraction index of this uninvolved region was 79% of normal (p < 0.005) (14).

The two modes of function in the noninfarcted myocardial segments revealed by echo are pathophysiologically important. First, in uncomplicated infarctions these segments seemed to contract unnecessarily vigorously probably under excessive adrenergic drive (14). Use of beta blocking drugs in these patients would logically protect markedly ischemic but not yet infarcted segments (5). Secondly, in large infarctions the vigorous compensating motion of the noninfarcted segments is obviously necessary for adequate pump function and survival (14). All those patients who had severe pump failure or died failed to show compensatory motion of the noninfarcted myocardium. Inadequate segmental response occurred even despite therapeutic inotropic support (13, 14). In this setting of failing uninvolved segments, even a small reinfarction carries a poos prognosis. These implications of the functional state of the noninfarcted segments have been so far largely overlooked in acute myocardial infarction.

contribution of individual segments to the overall left ventricular function which has not been possible so far non invasively The accuracy of technique in locating and quantifying either noncontractile or hyperfunctioning segments has been convincingly documented in the correlative studies with electrocardiogram cineangiographic analysis and autopsy data discussed above (4 10 11 12 13 14) (Fig 1)

Abnormal wall motion of the infarcted region occurred in each of the 30 consecutive patients with acute myocardial infarction (4) Asynergy was seen during the first hours of infarction and was often noted to precede the Q wave development in the serial ECG Serial studies were made on 24 patients during the first week in hospital (12) In anterior infarctions the asynergic contraction was generally maximal already on the 1st day The amplitude of the systolic paradoxical outward motion of the infarcted segment was 3 2 ± 3 0 mm without any later improvement Instead the border areas showed some improvement in 4 of the 8 anterior infarctions

In posterior infarctions paradoxical motion was an exception nevertheless a remarkable reduction of wall motion occurred at the posterior infarcted sites in every patient (4 3) The wall motion was most commonly akinetic the lowest wall motion mean amplitude of 1 9 ± 2 3 mm was seen on the 3rd postinfarction day (13) However no recovery has been observed in those patients with fatal infarction (13 15) The number of sites showing abnormal motion was smaller in posterior infarctions where the wall motion was most commonly akinetic (13)

The above differences in the regional performance between the anterior and posterior infarctions are in good agreement with the enlargement of the left ventricle in these groups (13) The left ventricular cavity size was enlarged in 62% of the 30 consecutive patients Such loss of segmental left ventricular function (6) agrees nicely also with the haemodynamic dysfunction which is more serious in anterior than in posterior infarctions (16)

QUANTITATIVE ASSESSMENT OF REGIONAL WALL MOTION

Mechanical performance of the left ventricular segments related well with the clinical severity of acute myocardial infarction Two basic factors operate here size of the asynergic region and the compensating ability of the noninfarcted myocardium The echoventriculographic contraction index by uniting these two factors clearly separated the patients with uncomplicated and moderately

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FURTHER APPLICATIONS

Recently the ultrasound technique has been a highly rewarding tool in experimental studies on the effects of pharmacological interventions in acute myocardial infarction (17) We have applied this concept in patients with acute myocardial infarction (5) The directional changes taking place in the ST segment mapping were noted to agree with the segmental wall motions visualized by echo The ischemic zones bordering the infarction instantaneously showed either stronger contraction or more marked dysfunction along with increase or decrease of ST segments deviations or chest pain (5) The myocardial segmental function reveals the effects of drugs on left ventricular dynamics instantaneously and more sensitively than the haemodynamic changes In patients with ongoing ischemic state this technique seems to detect very sensitively and rapidly any favourable or deleterious effert of a drug intervention

ACKNOWLEDGEMENT

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INTRODUCTION

M-mode echocardiography has proven to be a valuable method for estimating ventricular volume and describing various parameters of ventricular func tion in the symmetrically contracting normally shaped left ventricle (1 5) The M-mode echocardiogram provides the basic data from which these determinations are generated by recording the path of the ultrasonic beam as it traverses the left ventricular cavity from the endocardial surface of the interventricular septum to the corresponding endocardial surface of the left ventricular posterior wall In order to relate this basic distance or di mensions to global left ventricular size or function a number of assumptions must first be made It must be assumed that 1) the echocardiographic diameter of the ventricle represents a true minor dimension or axis of the ventricular chamber 2) the left ventricle is circular in its short axis configuration and hence the measured minor dimension is equal in all planes 3) the left ventricle conforms to a selected geometric shape in which the minor dimension measured from the echocardiogram bears a fixed relationship to the major or long axis of the geometric model and 4) that the function of the ventricle in the area recorded is reflective of overall left ventri cular function (6)

In the majority of cases these assumptions have proven to be essentially correct and hence estimation of left ventricular volume and function from a single minor dimension of the ventricle valid In specific clinical situa tions however the shape of the ventricle may be altered so that it no longer conforms to the assumed geometric model In these cases data rela tive to left ventricular volume and global function based on the previously noted assumptions will of necessity be inaccurate (5 6)

Changes in ventricular shape may be either symmetric affecting the entire left ventricle or localized to a specific portion of the ventricle When there is a change in overall ventricular shape the recorded echocardiographic dimension will also be effected In this regard Teichholz et al (7) noted an increase in the length to diameter ratio in small ventricles and a corresponding decrease in this ratio in larger more spherical ventricles Since the length/diameter ratio and, hence shape was a function of the dia meter (or echocardiographic dimension) the variation in shape could be appreciated and corrected for appropriately

CROSS-SECTIONAL ECHOCARDIOGRAPHIC EVALUATION OF CHANGES IN VENTRICULAR SHAPE IN THE ISCHAEMIC AND NON ISCHAEMIC LEFT VENTRICLE

A E WEYMAN,

From the Krannert Institute of Cardiology the Department of Medicine Indiana University School of Medicine and the Veterans Administration Hospital Indianapolis Indiana

SUMMARY:

M-mode echocardiography is a useful method for estimating left ventricular volumes and determining multiple parameters of left ventricular function in the symmetrically contracting normally shaped ventricle In many clinical situations however the shape of the ventricle may be altered or distorted in such a way that the basic M-mode diameter or dimension of the ventricle is no longer reflective of overall left ventricular volume or function

Cross-sectional echocardiography is a valuable method for detecting abnormalities in left ventricular shape and thereby defining those cases in which the M-mode method may not accurately reflect ventricular size or performance In this report two examples of abnormalities in ventricular shape are described These include the marked alteration in left ventricular conformation which occurs when aneurysm formation complicates ischemic heart disease and the more subtle changes in ventricular shape seen in patients with both absolute and relative right ventricular volume overload due to alteration in septal position These examples illustrate the value of cross-sectional echocardiography in defining abnormalities of left ventricular shape indicating situations in which the M-mode ehocardiographic determinations of ventricular volume and function may be misleading and explaining changes in the patterns of wall motion observed by M-mode echocardiography which are due to alterations in the shape of the left ventricle

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When change in ventricular shape is localized however it may either not effect the echocardiographic dimension or produce an effect which is not proportionate to the magnitude of the overall structural abnormality In these cases it will not be possible to appropriately assess the ventricular volume using the M-mode echocardiographic dimension or perhaps more singificantly to recognize the fact that this error has occurred The most common example of this is the patient with ischemic heart disease in whom a large area of ventricular dyskinesis or aneurysm formation may be present and yet in whom the standard echocardiographic dimension at the base of the heart may be normal In this manuscript we will discuss the role of cross sectional echocardiography in detecting localized abnormalities of left ventricular shape which may either be inapparent on the M-mode record or when present may be unappreciated as being due to a change in the shape of the ventricle

1 ABNORMALITIES OF LEFT VENTRICULAR SHAPE - ISCHEMIC HEART DISEASE

The most striking distortion in left ventricular shape is the ventricular aneurysm These aneurysms by definition distort both the systolic and diastolic shape of the ventricle and may vary in size from small functionally insignificant localized abnormalities to massive distortions of ventricular structure which underly severe cardiac decompensation Since aneurysm formation may complicate as many as 10 % of acute transmural myocardial infarctions and underlie such major complications as recurrent ventricular tachyarrhythmias systemic emboli and intractable congestive heart failure all of which adversely effect prognosis their detection is of major importance (8 9 10)

The M-mode echocardiogram has not proven to be a useful method for detecting ventricular aneurysms Despite the common occurance of these lesions data suggesting that the M-mode technique might detect aneurysms has appeared only in the form of isolated case reports (11 12) This occurs because aneurysms arise most commonly in areas of the ventricle such as the cardiac apex which are poorly recorded by the M-mode system In addition in order to appreciate the change in shape of any geometric figure it is generally necessary to be able to visualize the spatial configuration of the entire figure and not merely a localized portion

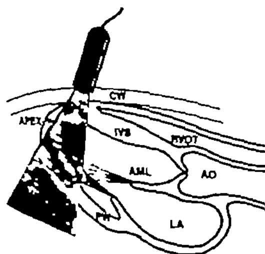


Fig 1 Cross-sectional echocardiographic recording of a long axis of the cardiac apex The normal tapering of the endocardium in the region of the cardiac apex together with the separation between the endocardial and epicardial interfaces reflective of wall thickness are apparent CW = chest wall IVS = interventricular septum RVOT = right ventricular outflow tract AO = aorta AML = anterior mitral leaflet LA - left atrium PW = posterior left ventricular wall

The advent of two-dimensional or cross sectional echocardiography enhanced our ability to detect ventricular aneurysms in several ways First as previously noted the cross sectional technique expands greatly the area of the heart which is available for examination By adding the cardiac apex as well as the medial and lateral walls of the left ventricle to the areas available for study this technique permits examination of the total left ventricle The ability to record the cardiac apex is of particular importance since fully 80% of coronary artery disease associated aneurysms will involve this area Secondly by displaying the accoustic data in a spatially oriented format the configuration of the long and short axes of the ventricle can be visualized and distortions in shape appreciated by their inappropriate relationship to more normal adjacent areas and/or variation from established normal ventricular configuration Finally by adding dynamic motion to the display differences in contraction patterns between adjacent areas can be observed which further highlight spatial distortion

Two earlier reports indicated that localized areas of asynergy or aneurysmal dilatation could be detected in selected patients using the B-mode scanning technique Teichholz et al (13) recorded B-mode scans of the left ventricle in 14 patients with localized ventricular asynergy and demonstrated a good correlation between the echocardiographic and angiocardiographic detection of these regions Similarly Yoshikawa et al (14) although unable to detect ventricular aneurysms using M-mode echocardiography were able to visualize areas of ventricular distortion in each of 15 patients using the B-mode scanning technique In a more recent study to examine the ability of real time cross sectional echocardiography to

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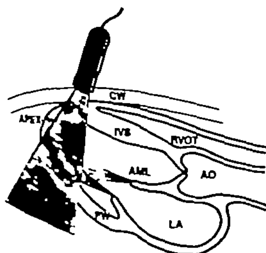


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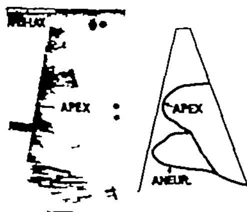


Fig 4: Long axis cross-sectional study of the cardiac apex and posterior wall demonstrating a larg posterior wall aneurysm. This aneurysm extended from the area of the papillary muscle to the AV-ring at the base of the heart. (From Weyman A E et al Detection of Left Ventricular Aneurysms by Cross-Sectional Echocardiography Circulation, 54:936 1976)



Fig 5 Left ventricular angiogram corresponding to the cross-sectional study in fig 4 Again the large aneurysm of the posterior wall of the ventricle is apparent (From Weyman A E et al Detection of Left Ventricular Aneurysms by Cross-sectional Echocardiography Circulation 54 936 1976)

there is initial motion of the apex toward the base of the heart together with symmetrical motion of the anterior and posterior left ventricular walls inward toward the geometric center of the ventricle In contrast in patients with apical aneurysms a clearly defined localized interruption in the dias tolic configuration of the left ventricular apex was noted This distortion in shape either remained constant or increased during ventricular systole

Fig 2 is a recording from a patient with a large anteroapical aneurysm il lustrating the change in ventricular shape seen with these lesions The right hand panel of this figure is a line drawing which compares the observed pattern of left ventricular apical shape (solid line) with the expected normal contour of the left ventricular apex (interrupted line) Fig 3 is an angiographic recording of the left ventricle from the same patient illustrating the similarity of apical contour recorded by these two imaging techniques

Although the cardiac apex is the area most frequently involved in ventricular aneurysm formation these lesions may occur in any area of the left ventricle Fig 4 is a cross sectional recording from a patient with an extensive posterior inferior aneurysm This aneurysm produces a marked alterati

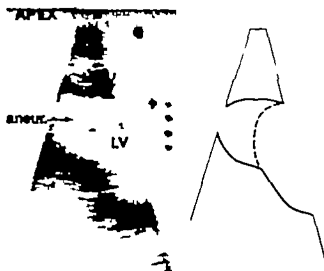


Fig 2 Long axis cross-sectional study of the left ventricular apex from a patient with a moderately large apical aneurysm The tip of the apex is to the left of the figure while the body of the left ventricle is to the right The vertical arrows indicate the junction of aneurysmal segment with the normal left ventricle The solid line indicates the recorded contour of the left ventricular apex while the interrupted line indicates the expected contour if the normal curvature of the body of the left ventricle were extended. Interruption of the normal curvature of the left ventricle by the ventricular aneurysm is apparent (From Weyman et al Detection of Left Ventricular Aneurysms by Cross-Sectional Echocardiography Circulation 54 936 1976)



Fig 3 Left ventricular cineangiogram corresponding to the cross-sectional study in fig 2 The apex in the angiographic study is reversed in comparison to the cross-sectional recording The sector superimposed on this angiogram illustrates the relationship of the 30° scan to the left ventricular apex with the transducer placed directly over the apical area The area of the ventricle encompassed in this 30° sector corresponds to the similar area in the sector in fig 2 (From Weyman A E et al Detection of Left Ventricular Aneurysm by Cross-Sectional Echocardiography Circulation 54 936 1976)

detect ventricular aneurysms we studied 31 consecutive patients with angiographically proven left ventricular aneurysms (15) In this study 87 % of the aneurysms were confined to or or involved the cardiac apex In each of these 31 cases it was possible to visualize the aneurysm with the cross sectional technique thus permitting its presence location and in the majo rity of cases extent to be determined Fig 1 is a cross sectional recording of the cardiac apical area illustrating the normal configuration of the en docardial and epicardial surfaces myocardial thickness and tapering of the ventricular myocardium in the region of the apex During normal contraction

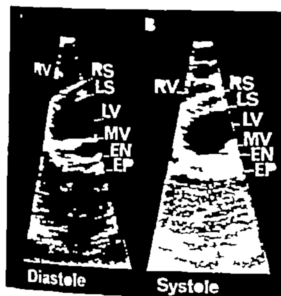


Fig 8 Normal short axis cross-sectional study of the body of the left ventricle at the level of the mitral valve The left hand panel is recorded during diastole and illustrates the normal circular configuration of the left ventricle and interventricular septum In the right hand panel recorded during systole there is progressive inward motion of the entire endocardial surface of the left ventricle toward the geometric center of the ventricular cavity with diminution in cavity size and increase in ventricular myocardial thickness RV = right ventricle RS = right side of the interventricular septum LS = left side of the interventricular septum LV = left ventricular cavity MV = mitral valve EN endocardium EP = epicardium (From Weyman A.E et al Mechanism of Abnormal Septal Motion in Patients with Right Ventricular Volume Overload. Circulation 54 179 1976)

tional system by defining the subgroup of patients with distortion in ventricular shape produced by ventricular aneurysms adds directly to our clinical knowledge and also is of indirect value by helping to exclude patients in whom M-mode estimations of ventricular function would be misleading

2 ABNORMALITIES OF LEFT VENTRICULAR SHAPE IN THE NON ISCHEMIC LEFT VENTRICLE

In addition to abnormalities of left ventricular shape occurring as a result of aneurysmal bulging of the left ventricular wall significant change in ventricular shape may also be produced by extrinsic compression or invagination of the left ventricle This type of abnormality of shape is most commonly produced by alteration in the position of the interventricular septum The original indication that abnormalities of ventricular shape might be due to alteration in septal position arose from the observation that in patients with right ventricular volume overload and paradoxical septal motion the left ventricular internal diameter frequently increased in the early portion of systole If in thesecases the ventricular diameter was an appropriate indicator of left ventricular volume then the volume of the ventricle would be increasing rather than decreasing during this phase of the cardiac cycle

Since an increase in volume during systole was impossible it was concluded that the ventricular diameter was no longer reflective of the ventricular volume and hence that a change in ventricular shape must have occurred

LV-LA

LV

Fig 6 Long axis cross-sectional scan of the body of the left ventricle demonstrating a small circular echo-free space beneath the posterior wall of the left ventricle with apparent continuity between the echo-free space and the cavity of the left ventricle (From Esteves C M et al Detection of Left Ventricular Diverticulum by Cross-Sectional Echocardiography Chest 69 644 1976)

AO

Fig 7 Long ventricular angiogram demonstrating a small localised diverticulum of the inferior wall of the left ventricle corresponding in appearance and location to the cross-sectional scan recorded in fig 6 (From Esteves et al Detection of left ventricular diverticulum by cross-sectional echocardiography Chest 69 644 1976)

in the posterior surface of the left ventricle extending from the posterior papillary muscle to the AV ring and involving the entire posterior surface of the ventricle Fig 5 is an angiographic recording from the same patient again illustrating the similarity in appearance of the aneurysm by angiography and cross sectional echocardiography

In addition to large coronary artery disease associated aneurysms it is also possible to record more discrete alterations of left ventricular shape (16) Fig 6 and 7 are a cross sectional scan and left ventricular angiogram from a patient with a small congenital left ventricular diverticulum The diverticulum as well as its communication with the left ventricular cavity are apparent from the cross-sectional recording

When the M-mode recordings in the same group of patients were examined the presence of an aneurysm based on an increase in ventricular diameter at the apex compared to the standard basal dimension was suggested in only 47 % of the cases (15) Furthermore these criteria were only applicable to patients with apical aneurysms with the result that aneurysms localized elsewhere in the ventricle were undetected by the M-mode technique Thus the cross sec

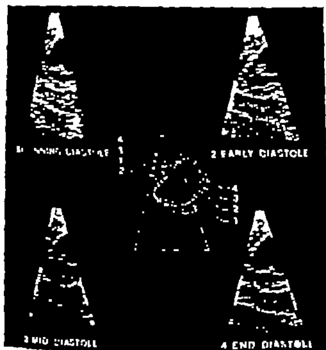


Fig 10 Serial short axis cross-sectional echograms of the body of the left ventricle in the region of the mitral valve beginning at end systole and extending through the diastolic filling period to end diastole The line drawing in the center of the figure illustrates the relative positions of the left ventricular endocardium at the various portions of the diastolic filling phase At the end of systole the left ventricle is in its normal circular configuration (1) Immediately following at the onset of diastolic filling (2) there is a marked inward motion of the interventricular septum toward the body of the left ventricle which changes the shape of the left ventricle As diastole progresses (3 and 4) the ventricle gradually returns to its more normal circular configuration. This return of the ventricle to normal shape is produced by gradual anterior and rightward motion of the interventricular septum back away from the body of the left ventricle toward its normal position (i e curving in toward the cavity of the right ventricle) The initial diastolic change in septal position reflects the rapid initial flow of blood into the right ventricle while simultaneous inflow into the left ventricle is retarded by the narrowed mitral valve orifice This creates a relative right ventricular volume overload during initial diastole which alters septal position and ventricular shape (From Weyman A.E et al : Mechanism of Paradoxical Early Diastolic Septal Motion in Patients with Mitral Stenosis A Cross-Sectional Echocardiographic Study Amer J Cardiol (in press)

produces a marked alteration in the position of the septum in space These illustrations suggest that if one were to record a normal diastolic dimension of the left ventricle in a patient with a right ventricular volume overload the marked change in position of the septum would negate any attempt to rela te this dimension to left ventricular volume since the shape of the ventricle no longer conforms to the geometric model on which this volume data is based

A similar phenomenon occurs in patients with mitral stenosis In these pati ents there is frequently a prominent abnormal or paradoxical motion of the interventricular septum occurring at the onset of ventricular diastole which corresponds to the maximal point of opening or E point of the mitral valve In study of 36 patients with mitral stenosis with a variety of associated le- sions we observed that this marked paradoxical or diastolic motion of the

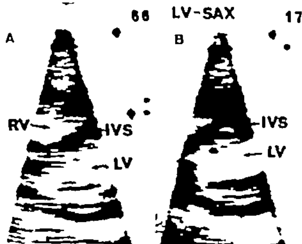


Fig 9 Short axis cross-sectional study of the left ventricle from a patient with marked right ventricular volume overload In Panel A there is marked inward bending of the interventricular septum away from the right ventricle and inward toward the left ventricle such that the left ventricular cavity assumes a half moon appearance during diastole Systolic contraction (Panel B) causes a return to the normal circular shape of the left ventricle This change in configuration of the ventricle from diastol to systole results in a marked anterior or paradoxical motion of the interventricular septum in space (From Weyman A E et al Mechanism of Abnormal Septal Motion in Patients with Right Ventricular Volume Overload Circulation 54 179 1976)

To examine this hypothesis the short axis configuration of the ventricle was examined in a group of patients with right ventricular volume overload and paradoxical septal motion (17) In this study it was noticed that when examined with the plane of the cross-sectional probe aligned parallell to the short axis of the left ventricular cavity the normal ventricle has a relatively circular configuration during diastole During systole the walls of the ventricle move symmetrically inward toward the geometric center of the ventricle During this contraction sequence the circular configuration of the ventricle is maintained (Fig 8) In contrast in patients with right ventricular volume overload the position of the septum during diastole was shifted away from the right ventricle and in toward the cavity of the left ventricle This change in septal position altered the shape of the left ventricle during diastole from circular to flattened or half moon During systole the rapid increase in left ventricular pressure forced the septum back in toward the right ventricle causing a return of the left ventricle to its normal circular configuration This change in septal position and ventricular shape from diastole to systole produced a net anterior or paradoxical motion of the septum in space Fig 9 is a recording from a patient with marked right ventricular volume overload In the left hand panel recorded during diastole the interventricular septum curves aqay from the right ventricle and bulges inward toward the left ventricle This changes the shape of the left ventricle from circular to kidney shape or half moon in configuration In the systolic panel to the right the ventricle has returned to a normal circular configuration This change in shape of the ventricle from systole to diastole

the left ventricle had returned to its normal shape and systolic contraction proceeded in a normal fashion

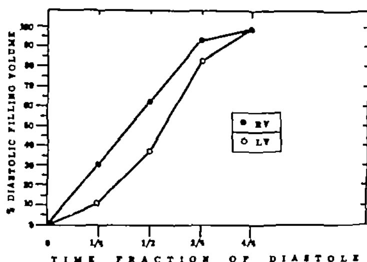
In order to determine the underlying causes of this phenomenon we divived these patients into those with and without a change in left ventricular diastolic shape All hemodynamic parameters including cardiac output left atrial pressure pulmonary artery pressure and left and right ventricular end diastolic pressures were similar for both groups Only the mitral valve orifice size was significantly different between the two groups with those patients with an abnormal initial diastolic shape having smaller mitral valve areas In addition those patients with no abnormality of left ventricular diastolic shape had a far greater incidence of concomittant volume load on the left ventricle such as mitral insufficiency or aortic insufficiency It was concluded from these data that the abnormality in diastolic shape in mitral stenosis was due to unequal filling of the two ventricles due to the stenotic lesion At the onset of diastole the right ventricle fills rapidly due to the unimpaired tricuspid valve flow while left ventricular filling is restricted by the narrowed mitral valve orifice This produces a relative right ventricular volume overload in initial diastole and thrusts the septum in towards the left ventricle As diastole progresses left ventricular filling is belatedly completed thus equalizing the volumes of the ventricles and returning the septum gradually toward a more normal position Fig 11 illustrates the relative rates of right and left ventricular filling and septal motion pattern in a patient with combined mitral stenosis and right ventricular volume overload

These data suggest that there are a number of situations in which the shape of the ventricle may vary from normal during at least part of the cardiac cycle It is also apparent that any method used to calculate ventricular volume or assess ventricular function which does not take into account these changes in ventricular shape will be subject to error

CONCLUSION

This report therefore suggests that cross-sectional echocardiography is a valuable method for detecting changes in left ventricular shape in the ischemic and non-ischemic left ventricle Abnormalities of shape produced by evagination of the left ventricular wall in patients with ventricular aneurysms and invagination of the wall produced by change in left ventricular septal

septum was present on M-mode recording in 25 cases (18) Cross sectional studies in this group of patients revealed that coincident with the diastolic septal motion abnormality there was a change in left ventricular diastolic shape produced by a *shift in septal position away from* the right ventricle and in toward the left ventricle Fig 10 is an example of the diastolic motion pattern of the interventricular septum during ventricular filling As ventricular filling continued the septum gradually *returned toward* a more normal circular configuration so that by the onset of ventricular systole



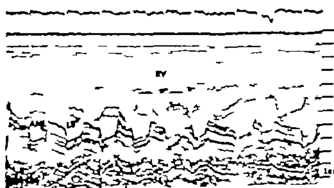


Fig 11 M-mode echocardiographic recording of the intraventricular septum and left ventricular cavity from a patient with combined mitral stenosis and right ventricular volume overload. In this figure the intraventricular septum moves paradoxically or anteriorly during systole and posteriorly during diastole This abnormal initial diastolic septal motion again reflects the relative volume flow into the two ventricles in the initial portion of diastole Because of the combined relative and absolute volume load on the right ventricle the septum fails to return to its normal position at end diastole and hence the shape of the ventricle remains abnormal Ventricular systole therefore occurs with the ventricle still in an abnormal configuration with systolic contraction back towards its normal configuration re-establishing the normal shape of the ventricle and moves resulting in the paradoxical systolic motion of the interventricular septum In the upper portion of this panel right and left ventricular filling expressed as a percentage of total filling of the ventricle are recorded for each of the four qarters of diastole It is evident that due to obstruction to mitral valve inflow the filling of the left ventricle is significantly delayed in initial diastole relative to filling of the right ventricle At end diastole both ventricles have filled to a hundred percent of their diastolic volume and therefore percent filling is equalled. Due to the associated right ventricular volume overload however the absolute volume of the right ventricle in this case would be greater than that of the left ventricle

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position can be equally well evaluated Much of the data relative to septal position although previosly suspected could not be proven without the abi lity to view the short axis configuration of the left ventricle This short axis view provides new and unique data which has heretofore been unobtainable by any invasive or noninvasive method It is hoped that these improved methods of visualizing the dynamic geometry of the left ventricle will provide more accurate echocardiographic assessment of cardiac structure and function

ACKNOWLEDGEMENT

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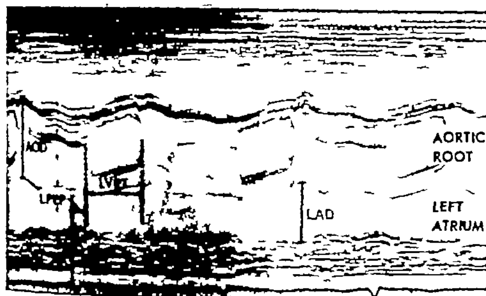


Fig 1. Echocardiogram of the aortic root showing LPEP and LVET measurements AOD aortic root diameter LAD = left atrial dimension.

since these estimations are just further mathematical elaborations of the same measurements and thus more prone to errors

Systolic time intervals have been measured from high speed recordings of the echoes from the aortic leaflets (5 10) Left ventricular pre-ejection period (LPEP) is measured from the beginning of the QRS-complex to the opening of the leaflets and LVET from the opening to the closing of the leaflets (fig 2) This is a more direct and in children an easier way of obtaining the systolic time intervals than the conventional method using electrocardiogram phonocardiogram and external carotid pulse tracings

LVET varies strongly with heart rate (9) If the expected LVET for the observed heart rate is calculated from the formula LVET 372 52 1 19 x heart rate(unpublished material)and the actual LVET then is expressed as percent of the expected LVET% the parameter is made independent of heart rate (7) The quotient LPEP/LVET is another widely used parameter independent of heart rate (1 3 4)

Measurements were compared to normal values obtained from a group of 53 children without heart disease (age 1 19 years) Δ LVID = 34+8 % Mean Vcf 33+0 38 circ/sec LPEP/LVET 0 27+0 08 LVET% 100+8 % (all values given as mean + 2 SD)

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ECHOCARDIOGRAPHIC ASSESSMENT OF LEFT VENTRICULAR FUNCTION DURING THE POSTOPERATIVE PERIOD IN CHILDREN OPERATED ON BECAUSE OF CONGENITAL HEART DISEASE

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During the last 18 months children operated on because of congenital heart disease in Lund have been followed by repeated echocardiographic examinations during the postoperative period to assess the changes induced in left ventricular function by the operation

As parameters of left ventricular function contractility indices and systolic time intervals have been used (2 6 8) The contractility indices are derived from measurements of the left ventricular internal dimensions in end systole ($LVID_s$) and in end-diastole ($LVID_d$) $LVID_d$ is measured at the beginning of the QRS-complex and $LVID_s$ as the shortest distance between the left side of the septum and the endocardium of the posterior wall of the left ventricle in end-systole (fig 1) From these measurements shortening fraction or ΔLVID is calculated as $(LVID_d\ LVID_s)/LVID_d$ Mean velocity of circumferential fiber shortening (Mean Vcf) is derived from the same measurements and the left ventricular ejection time (LVET) Mean Vcf=$(LVID_d\ LVID_s)/LVID_d \times LVET$ We have not attempted to calculate volumes and cardiac output

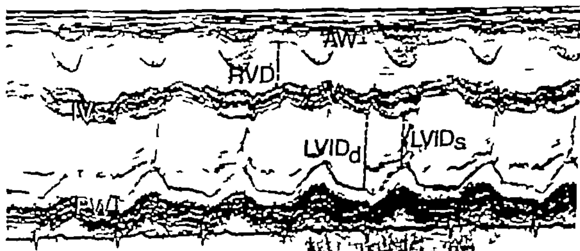


Fig 1 Echocardiogram of the left ventricle showing sites for measuring $LVID_d$ and $LVID_s$ AW = anterior wall RVD = right ventricular dimension IVS = interventricular septum PW = posterior wall of the left ver

patients with AV-commune (the complete form of endocardial cushion defect) showed a marked decrease in left ventricular function post-operatively Patients who where operated on because of ASD aortic stenosis (AS) and pulmonary stenosis (PS) that is with very short or no cardio pulmonary by-pass showed normal function postoperatively Two patients operated on because of coarctation of the aorta (CA) were included to evaluate if the thoracotomy as such would influence heart function but no decrease could be discerned The patients with aortic stenosis usually had a high Δ LVID preoperatively which actually increased in the immediate postoperative period and then slowly normalized

Fig 3 shows the changes in left ventricular function postoperatively in an 8-year-old boy operated on with correction of Fallot s anomaly and closing of a Waterston shunt Preoperative function is normal and immediately after the operation Δ LVID Mean Vcf and LVET% decreases and

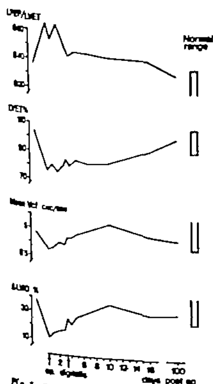


Fig 3 Parameters of left ventricular function (LPEP/LVET LVET% Mean Vcf ΔLVID) pre- and postoperatively in an 8-year-old boy operated on with correction of Fallot s anomaly and closure of a Waterston shunt.

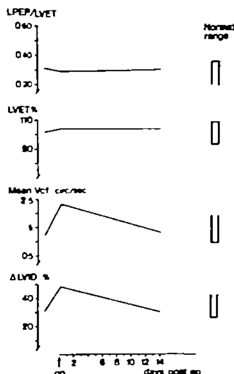


Fig 4: Parameters of left ventricular function (LPEP/LVET LVET% Mean Vcf Δ LVID) pre- and postoperatively in a 7-year-old boy operated on with correction of a coarctation of the aorta.

TABLE 1: Clinical material - diagnosis number of patients and postoperative left ventricular function

DIAGNOSIS	NUMBER	POSTOPERATIVE LV-FUNCTION
Fallot + Waterston	6	↓
Fallot	8	↓
ASD + VSD	1	↓
VSD + PULM BANDING	9	↓↘
VSD + PS	5	↘
VSD	5	↘
ASD + PS	1	→
ASD	14	→
MS	1	↓
AV - commune	2	↓
AS	6	→
PS	2	→
CA	2	→

The children have been examined preoperatively and on the day of the operation or the following day After that examinations have been done daily for a period or with longer intervals depending on the cardiac status and the speed of recuperation

So far 62 children have been followed Table I shows the number of patients in each group and also gives a rough estimate of the decrease in left ventricular function postoperatively for each group Patients undergoing more extensive operations such as correction of Fallot s anomaly and closing of a Waterston shunt correction of Fallot s anomaly without previous shunt closing of an atrial septal defect (ASD) + a ventricular septal defect (VSD) closing of a VSD and debanding of the pulmonary artery all showed a marked decrease in left ventricular function In the group operated on with closing of a VSD and debanding there is a less marked decrease in left ventricular function in those patients where the band could be removed without damaging the pulmonary artery and the operation thus was shorter and less complicated Patients operated on with closure of a VSD or closure of a VSD and removal of an infundibular pulmonary stenosis (PS) showed intermediate decrease in left ventricular function The patients with complicated operations as one boy reoperated upon because of a mitral stenosis (MS) and two

There seem to be a close correlation between the degree of post-operative decrease in left ventricular function and the extent of the operation especially concerning cardio-pulmonary by-pass time aorta clamping time and problems encountered during the operation but this has to be evaluated further

For natural reasons we have not followed many patients who have died soon after the operation One patient who was operated on with correction of Fallot s anomaly died on the second post-operative day and that patient had a LVET% of 60% immediately post-operatively The same low value was recorded in a patient operated on because of VSD and pulmonary hypertension who also died on the second post-operative day Values of LVET% as low as 60% thus seem to indicate a very grave prognosis Included in the group of patients with Fallot is one girl who initially went down in LVET% to 85%, the value remaining there for about one week but then decreasing to 67% before the patient died in complications to the operation including a bacterial pericarditis

As was mentioned before pathological septal movement can often be seen postoperatively also in patients who had normal septal movement before the operation Often the movement pattern returns to normal within the first post-operative week but the septum may also remain immobile On the third or fourth post-operative day an echo-free space is often found behind the heart probably representing fluid in the opened pericardium This is seen in patients progressing normally and without signs of post-cardiotomy syndrome The echo-free space usually disappears within ten days If on the other hand a similar echo-free space is noticed on the day of the operation or early the next day it usually represents an on-going hemorrhage and we have seen several cases where re-operation was necessary The size of the left atrium usually diminished directly postoperatively after closing of a VSD and if the size increases again it is often the first sign of a disrupted patch

Thus the post-operative echocardiographic examination can be a value in detecting complications apart from the estimation of left ventricular function The degree of postoperative decrease in left ventricular function is an indicator of how well the myocardium withstood the operation and can be used to evaluate different operative techniques and maybe to predict the outcome

LPEP/LVET increases as would be expected when myocardial function is impaired On the third day the boy was digitalized and when examined 1 hour after the initial parenteral dosis of digitalis left ventricular function actually seemed to have improved For comparison fig 4 shows left ventricular function pre and postoperatively in a 7-year-old boy operated on with correction of a coarctation of the aorta- here no decrease in left ventricular function could be discerned

On the parameters used to assess left ventricular function Mean Vcf seems to be the least sensitive with its large normal range The other parameters are influenced about equally but LPEP/LVET is the one to normalize last usually over weeks to months During the immediate postoperative period LVET% is the parameter that is most convenient to use when comparing different groups of patients since Δ LVID and Mean Vcf can be unreliable if some patients in a group have inverse septal movement postoperatively and LPEP/LVET can be deranged due to the use of a pacemaker during the first postoperative days

TABLE II: Range of LVET% in the immediate postoperative period for different groups of patients

	POSTOP LVET % range
FALLOT + WATERSTON	64 - 84 %
FALLOT	66 - 90 %
VSD + PULM BANDING	68 - 83 %
OTHER DIAGNOSIS	70 - normal

Table II gives the range of LVET% in the immediate postoperative period in the different groups Only patients surviving the first postoperative week are included In the group operated on with correction of Fallot s anomaly and closing of a Waterston shunt LVET% decreased to 64% at the most and to 84% in the patient who withstood the operation the best Among the patients with Fallot s anomaly without previous shunt there is one patient who did not decrease in LVET% to more than 90% which is very close to the lower normal limit of 92% This was a girl who withstood the operation extremly well in all respects The patient coming closest to her had a lowest LVET% of 85%

PULMONARY VALVE MOTION IN VALVULAR PULMONARY STENOSIS IN CHILDHOOD

C REY AND J M LABLANCHE

From Service de Cardiologie Infantile Hôpital Calmette Lille France

SUMMARY:

Echocardiography tracings of the pulmonary valve was recorded in 16 patients with pulmonic stenosis (PS) ranging in ages from 6 to 14 years (average 10 years) 11 patients had an isolated PS and 5 had a PS associated with atrial septal defect

In 2 patients with mild PS (gradient 15 mm Hg) the depth of the a wave was normal: 3 and 4 mm

In 14 patients with moderate or severe PS (gradient 40 mm to 204 mm Hg) the maximal depth of the a wave was less than 6 mm in 2 patients and more than 6 mm in 12 patients (range 7 to 15 mm average 10 mm) The motion of both anterior and posterior pulmonary valve leaflets was well recorded in 3 patients with severe PS The a wave showed a posterior motion of the posterior leaflets and an anterior motion of the anterior leaflet This motion is due to the premature pulmonary valve opening

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Since the initial observations of pulmonary valve by echocardiography (3) the posterior motion after the atrial conctraction (a wave) has been well described The absence of a wave in severe pulmonary hypertension and the exaggerated leaflet motion in pulmonary stenosis has previously been reported (5 10 13) The purpose of this report is to evaluate the pulmonary valve motion following the atrial contraction in children with valvular pulmonary stenosis

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MATERIAL AND METHODS

The clinical material consisted of 3 groups of patients

Group I was composed of 16 patients with valvular pulmonary stenosis documented by cardiac catheterization studies Their ages ranged from 6 to 15 years the average being 10 years There were 8 males and 8 females Eleven patients had isolated valvular pulmonary stenosis 5 had pulmonary stenosis and ASD with a moderate left to right shunt ($QP/QS < 2$) At catheterization the systolic pressure gradient between the pulmonary artery and the right ventricle was mild in 2 cases (15 mm Hg) moderate in 13 cases (gradient 40 to 90 mmHg) severe in one case (gradient 200 mm Hg)

The echocardiographic patterns seen in patients of the first group were compared with those in the two other groups

Group II 20 normal patients age 5 to 15 years These patients did not undergo cardiac catheterization but clinical examination ECG and X ray were normal

Group III 20 patients age 6 to 15 years with isolated ASD documented by cardiac catheterization

All ultrasonic examinations were carried out using a commercially available echograph (EchocardioVisor Organon Teknika)

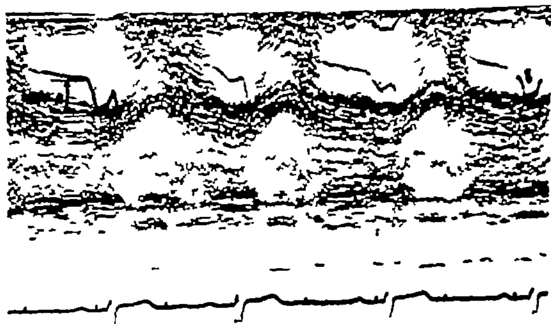


Fig 1 Child age 15 years with moderate pulmonary stenosis (gradient 60 mm Hg) Posterior pulmonary leaflet recording During the inspiration in the first and fourth complex from the left the "a wave depth is 15 mm The second complex was recorded during expiration and the a wave depth was normal



Fig 1: Child age 14 years with moderate pulmonary stenosis (gradient ?? mm Hg) Anterior and posterior pulmonary leaflets recording The anterior pulmonary valve leaflet moves anteriorly after atrial systole and posterior pulmonary valve leaflet moves posteriorly

A 5 MHz unfocused transducer was used to record the pulmonary valve echo Strip chart recordings were obtained with a Honeywell recorder

Pulmonary valve echocardiograms were obtained by the method previously described by Gramiak and al (3) The aortic root is identified and from this position the ultrasonic beam was then angled superiorly and laterally toward the left shoulder The depth of the a wave increased with inspiration. Therefore continuous pulmonary valve recording was performed during one respiration cycle in all patients Only maximal a wave depth was considered (Fig 1)

RESULTS

Group I: The a wave was 3 to 15 mm (average 9 mm) In the 2 cases with mild valvular pulmonary stenosis (gradient 15 mm Hg) the a wave was 3 and 4 mm. In the 13 cases with moderate stenosis (gradient 40 to 90 mm Hg) the a wave ranged 4 to 15 mm (average 10 mm) There was no difference about the a wave between the patients with isolated pulmonary stenosis and the patients with pulmonary stenosis and ASD In 8 patients with isolated pulmonary stenosis the a wave averaged 10 4 mm (range 4 to 15 mm); in the 5 patients with pulmonary stenosis and ASD the a wave averaged 9 6 mm (range 5 to 11 mm) In the patient with severe pulmonary stenosis (gradient 200 mm Hg) the a wave was only 7 mm Both anterior and posterior

leaflets were recorded in 3 cases with moderate stenosis (fig 2) After atrial contraction the anterior leaflet moved anteriorly and the posterior one moved posteriorly

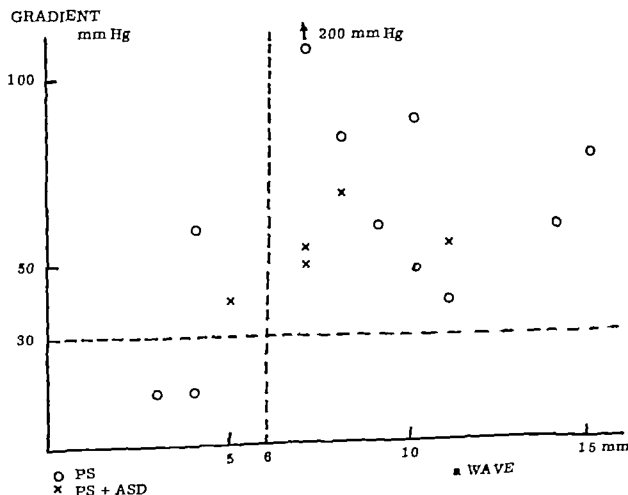
Group II and III During inspiration and expiration the maximal a wave was equal or inferior to 6 mm

DISCUSSION

The pulmonary valve is more easily located and recorded in children than in adults and more easily recorded if the pulmonary artery is dilated The pulmonic valve was well recorded in 16 of our 18 cases of valvular *pulmonary stenosis*

In 3 patients the anterior leaflet motion was recorded This motion is easily recorded in the newborns and in patients with pulmonary hypertension

TABLE I



or with important left to right shunt (4 10) On the other hand this anterior leaflet motion is rarely recorded in the other cardiac malformations In our three observations the transducer was in the second left interspace position So the ultrasonic beam is more perpendicular to the pulmonary artery and therefore both the anterior and posterior pulmonary leaflets are more easily recorded than in the third or fourth interspace position In addition the diastolic e-f slope the magnitude of the a wave seems less important to the second interspace than in the third one because the ultrasonic beam is more perpendicular

In normal adults the maximal a wave depth recorded by Weyman is 7 mm (9) Our study shows a maximal a wave magnitude of 6 mm in children

There is no correlation between the a wave depth and the systolic pressure gradient between the pulmonary artery and the right ventricle (table I) In one case with severe pulmonary stenosis (gradient 200 mm Hg) the a wave is only 7 mm and in 2 of 13 cases of moderate stenosis the a wave is normal But in the mild stenosis the a wave depth is within the normal range as Weyman has previously reported (9)

In the normal subjects the anterior and posterior pulmonary valve leaflets open after the onset of ventricular systole The right ventricular pressure is superior to the pulmonary artery pressure In the patients with pulmonary stenosis the a wave is a premature pulmonary valve opening following atrial contraction This fact is demonstrated by hemodynamic studies (2 7) In our study catheterization was not performed simultaneously with the echocardiographic examination However right ventricular pressure equals or exceeds pulmonary artery pressure at the peak of a wave causing the pulmonary valve to open (7) In echocardiographic tracings motion of the anterior and posterior pulmonary valve leaflets is symmetrical at the moment of the a wave in 3 patients

The anterior pulmonary valve leaflet is separated from the posterior leaflet after atrial systole and indicates that the large a wave reflects opening or doming of the valve However the maximal amplitude of this leaflet separation after atrial systole is the same as after ventricular contraction So this fact indicates that the large a wave is an opening of the valve and not doming

Pulmonary valve opening occurs during ventricular systole in the normal subject But an increase in right ventricular end-diastolic pressure to a level equalling or exceeding pulmonary artery pressure will produce opening of the pulmonary valve This right ventricular end diastolic pressure increase occurs in certain situations valvular pulmonary stenosis particularly during inspiration decreasie of right ventricular compliance

In Tetralogy of Fallot premature pulmonary valve opening has been already described at catheterization (1) but not at echocardiography because the pulmonary valve is rarely recorded

Premature pulmonary valve opening can be independent of atrial systole (7) but it is very rare This premature pulmonary valve opening was noted in constrictive pericarditis Loeffler's endocarditis Ebstein s anomaly with tricuspid regurgitation tricuspid regurgitation following tricuspid valvulectomy pulmonary regurgitation accompanied by atrial septal defect and *Valsalva aneurysm rupture into the right atrium (2 7 12) Premature opening* of the aortic valve in late diastole demonstrated by echocardiography in a patient with severe aortic regurgitation (6 8) was due to a *pressure equalization between the left ventricle and aorta*

We conclude that an augmented a wave in patients with moderate and severe pulmonary stenosis does reflect premature opening of pulmonary valve But this premature opening occurs in other situations and is not specific for pulmonary stenosis In children with valvular pulmonary stenosis the a wave is very often increased when the gradient is superior to 40 mm Hg *(12 of 14 children in our study)*

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ECHOCARDIOGRAPHY IN THE DIAGNOSIS OF SUBAORTIC STENOSIS

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During the routine echocardiographic examination of the heart using the M-mode scanning the outflow tract of the left ventricle is easily examined In the view seen by the ultrasound beam during this M-mode scanning the anterior border of the outflow tract consists of the interventricular septum and the posterior border of the anterior mitral leaflet (Fig 1) As a measurement of the width of the outflow tract ($LVOT_d$) we have taken the shortest distance between the left side of the interventricular septum and the anterior mitral leaflet in end-diastole as indicated on Fig 1

The patient material studied consists of all patients with a subaortic stenosis examined with echocardiography The patients with a hypertrophic obstructive cardiomyopathy are excluded The material comprises 13 patients aged 2 months to 13 years (mean and median age 7 years) Five of the

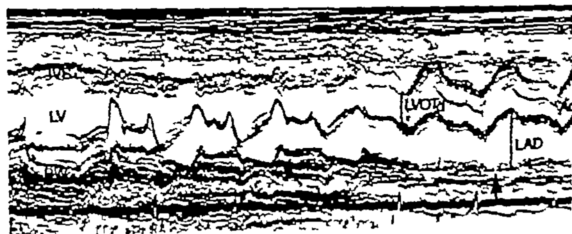


Fig 1 Echocardiogram obtained by M-mode scanning along the longaxis of the left ventricle (LV) up to the aortic root (Ao) in a child without heart disease The site of measurement of the left ventricular outflow tract dimension in end-diastole ($LVOT_d$) is indicated.

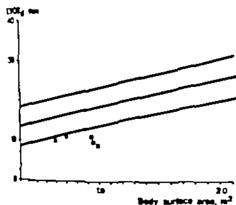


Fig 1. Diagram showing the left ventricular outflow tract dimention in end-diastole (LVOTd) in the patients with subaortic stenosis in relation to the normal values. The lines indicate the mean ± 2 SD. The patients with subaortic membrane are indicated by a circle, the patients with a fibro-muscular collar-like stenosis by a square and the patient with the obstruction caused by an abnormal papillary muscle by the triangle

patients had a subaortic thin membrane, seven patients a longer fibro-muscular collar-like stenosis and in one patient the stenosis was caused by a single abnormally placed papillary muscle of the mitral valve. The diagnosis was in all patients based on heart catheterization and angiocardiography. The diagnosis was further verified at operation in eight patients and at autopsy in the patient with the abnormal papillary muscle causing the stenosis.

It has previously been shown (Popp et al 1974) that an echo from a subaortic membrane can be obtained by echocardiography. Such an echo could not be obtained in any of our five patients with a membraneous subaortic stenosis despite prior knowledge of the diagnosis in four of them. The possibility of obtaining echoes from such a membrane depends on the spatial orientation of the membrane in relation to the ultrasonic beam.

The most constant abnormal finding in our patients was a narrow outflow tract of the left ventricle. All patients with a fibromusular collar-like stenosis had an outflow tract of the left ventricle more narrow than normal (Fig 2). Four of the five patients with a membraneous subaortic stenosis also had an outflow tract more narrow than normal (Fig 2). The most narrow outflow tract was found in the two months old boy with a stenosis caused by an abnormal papillary muscle (Fig 2). A M-mode scan from the left ventricle up to the aortic root from this patient is seen in Fig 3. The outflow tract of the left ventricle can be seen to be extremely narrow

Fig 3 Echocardiogram obtained by M-mode scanning from the left ventricle up to the aorta (Ao) in the patient with a subaortic stenosis caused by an abnormal papillary muscle The interventricular septum (IVS) is thickened. The outflow tract of the left ventricle (oblique arrow) is extremely narrow compared to the width of the aortic root The horizontal arrow points to the echoes from the mitral valve

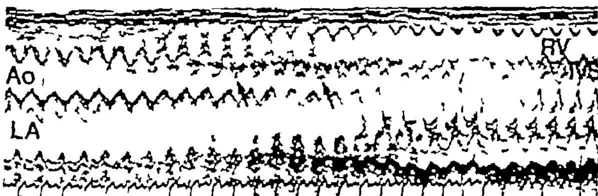


Fig 4 Echocardiogram obtained by M-mode scanning from the aorta (Ao) to the left ventricle in a patient with a subaortic stenosis of the fibromuscular collar-like type The oblique arrows point to the narrow outflow tract of the left ventricle The length of this stenosis cannot be estimated by this method.

In a M-mode scan along the outflow tract of the left ventricle the length of a subaortic stenosis cannot be determined since the length seen on such a recording also depends on the speed with which the scanning is performed (Fig 4) Information about the length of the stenosis can be obtained by

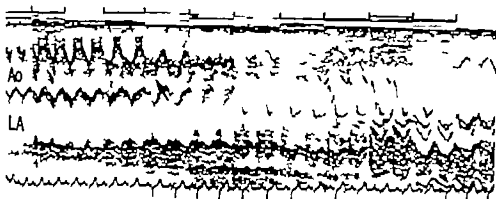


Fig 5 Echocardiogram obtained by single-element echocardio-tomography by use of a multi-element transducer on the same patient as in Fig 4 and with the transducer placed along the long-axis of the left ventricle The small markings on the top of the recording indicate the border between the echocardiograms obtained from each individual line on the multi-element transducer With the transducer used for this examination the distance between the level from which two adjacent short echocardiograms are obtained is 4 mm. It can thus be shown that this subaortic stenosis is short

two-dimentional echocardiography or by single-element echocardio-tomography by use of the multi-element transducer (Lundström and Hansson 1977) as shown on Fig 5 (the same patient as in Fig 4)

It has been described previously that an abnormal motion of the echoes from the aortic leaflets can be seen in patients with a subaortic stenosis (Davis et al 1974) Such an abnormal motion of at least one of the aortic leaflet echoes could be seen in all the nine patients where echocardiogram from the aortic root was of adequate quality to study the motion of the aortic leaflet echoes

In summary it seems possible to identify a localized subaortic stenosis by M-mode echocardiography in most patients The most important echocardiographic finding has been the demonstration of a narrow outflow tract of the left ventricle Identification of a subaortic thin membrane seems more unreliable The length of a subaortic stenosis cannot be provided by M-mode echocardiography but can be obtained by two-dimentional echocardiography

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TWO-DIMENSIONAL ECHOCARDIOGRAPHY IN ATRIOVENTRICULAR CANAL MALFORMATION A DIAGNOSTIC APPROACH

H A Y DRAULANS-NOË P J VOOGD C M LIGTVOET J RIDDER AND A C G WENINK

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SUMMARY

Two-dimensional echocardiographic studies were performed in 20 children with various forms of atrio-ventricular canal malformation Both sagittal and transverse cross-sections were evaluated The most typical finding in all patients was the visualization of the cleft anterior mitral leaflet (AML) represented by a diastolic break of AML echoes in the sagittal cross-section - In cases where the AML is attached to the interventricular septum varying degrees of left ventricular outflow tract narrowing and elongation were observed

In the transverse cross-section mitral-tricuspid alignment could be observed at the level of the aortic root The ventricular septal defect in complete AVC was visualized as an echo-free space between the common anterior leaflet and the interventricular septum

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The purpose of this study is to assess the value of multiple-crystal two dimensional echocardiography in children with various forms of atrioventricular canal malformation (AVC) In this report we describe features common to all patients including visualization of the characteristic cleft in the anterior mitral leaflet (AML) as well as specific findings in children with complete AVC The importance of adjusted transducer position is stressed and the advantages of continuously focussed multiscan system

TABLE 1

PATIENT MATERIAL

ATRIOVENTRICULAR CANAL MALFORMATION (20 CHILDREN)		
GROUP I	INCOMPLETE AVC	8 children
	ASD I	7 children
	VSD (of the AVC type)	1 child
GROUP II	ASD I + VSD	5 children
	no PH	(1 x Down s syndrome)
GROUP III	COMPLETE AVC	7 children
	with PH at systemic level	(6 x Down s syndrome)

ABBREVIATIONS AVC = atrioventricular canal ASD I ostium primum atrial septal defect VSD ventricular septal defect PH = pulmonary hypertension

MATERIAL AND METHODS

Twenty children with AVC malformation (table 1) ranging in age from 2 to 14 years (average 8 years) were examined with a prototype multiple crystal continuously focussed linear array echocardiographic system developed in the experimental echocardiographic laboratory of the Thoracic Center Rotterdam (2 3)

Eight patients had incomplete forms of AVC malformation (group I table 1) with an atrial septal defect of the primum type (ASD I) in 7 patients and a ventricular septal defect (VSD) of the AVC type in 1 patient Five patients had an ASD I with additional VSD but without significant pulmonary hypertension



Fig 1 Schematic representation of the abnormal motion pattern of the left AML in AVC Sagittal cross-section atrial septal defect of the primum type I diastole the lower mobile part of the superior (S) segment of the AML moves anteriorly and upwards into the left ventricular outflow tract (LVOT) while the inferior (I) segment moves in the opposite direction The upper part of the superior segment is less mobile due to its chordal attachments to the interventricular septum It forms the posterior border of the elongated narrow LVOT RV=right ventricle Ao=aorta LV=left ventricle LA left atrium

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(PH) (group II) So far one of these patients proved to have a complete AVC with central VSD at operation Seven patients had a complete AVC with PH at systemic level (group III) and Down s syndrome in 6 of them

Each patient had the typical clinical and electrocardiographic findings of AVC malformation which could be confirmed by left ventricular angiocardiography in 18 children

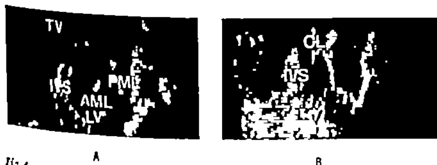
A 3.12 MHz 51 element transducer was used in all patients producing images at a frame rate of 80/sec and displaying a total of 80 lines of the oscilloscope. The real time images viewed on the oscilloscope were stored on video tape (4) and copied on 16 mm motion film and/or polaroid photographs

Sagittal and transverse cardiac cross sections were evaluated with the transducer placed respectively vertically along the left sternal border and horizontally in the fourth intercostal space with the superior crystal to the right.

RESULTS

SAGITTAL CROSS-SECTION

In patients with the AML attached to the interventricular septum (IVS) (group I and III) the AML seemed to consist of an immobile upper part (fig 1) forming the posterior border of the left ventricular outflow tract (LVOT) and a mobile lower part In systole the immobile upper part failed to move to a normal position posterior to the aortic root (fig 2) Most cha



A B

Fig 4 systolic transvers cross-section at the level of the left ventricular outflow tract

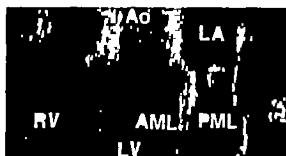
A. Atrial septal defect of the secundum type normal mitral - tricuspid discontinuity is well visualized.

B. Complete AVC showing mitral - tricuspid alignment The ventricular septal defect is visualized as an echofree space between the common anterior leaflet (CL) and the IVS

— tricuspid valve



A

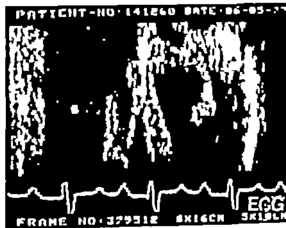


B

Fig 2 Normal sagittal cross-section (polaroid photo) A = diastole B = systole The anterior mitral leaflet (AML) moves anteriorly towards the interventricular septum (IVS) in diastole Systolic valve closure brings the AML to a position posterior to the root of the aorta RV=right ventricle LV=left ventricle LA=left atrium PML=posterior mitral valve



A



B



C

Fig 3 Sagittal cross-section atrial septal defect of the primum type
A Early diastole a break in anteri mitral leaflet (AML) echoes appears This is caused by the mobile part of superior segment (S) of the AML moving anteriorly and upwards into the left ventricular outflow tract while the ferior segment (I) moves in the opposi direction This diastolic break represents the cleft AML
B End-diastole
C Systole Both segments of the AML have approximated again the cleft is not visible Systolic posterior motion of the AML is reduced

DISCUSSION

Two-dimensional echocardiographic studies in patients with AVC malformation have been reported in the literature (1 7) including multiple crystal evaluation (5) These studies however are limited and we feel that better understanding of the anatomy and recent improvement in technique (3) has improved our possibilities for correct interpretation of the echocardiographic features in these patients

In AVC malformation the AML is not only malformed (being cleft) but also malpositioned due to absence of the atrioventricular septum (fig 5) and shows an abnormal motion pattern (fig 5 and 6) Both parts of the cleft AML are situated perpendicular to the IVS rather than parallel to it as in normally the case Its plane of motion is parallel to the IVS In order to visualize the abnormally placed AML and its motion pattern we adjusted our transducer position accordingly into a rather vertical plane of section In this position the echo beam will reach both segments of the AML and the diastolic cleft in between. The PLM will hardly be visualized as it is not reached by the echo beam.

Diastolic septal apposition and reduced posterior motion of the AML in the sagittal cross-section are well-established features in patients with AVC malformation both in M-mode scanning and two-dimensional techniques (5) Anterior displacement and reduced systolic posterior motion of the fixed part of the AML may result in varying degrees of the LVOT elongation and narrowing We feel that this may prove to give us some information on the severity of the anomaly as has been described for the shape of the LVOT on left ventricular angiocardiography (6)

The most characteristic observation however was the visualization of a diastolic "break in AML echoes in all our patients regardless of the type of the anomaly So far we have not encountered this feature in normal subjects nor in approximately 40 patients with various forms of congenital or acquired heart disease studied in the same period with the same technique We feel that this diastolic "break in AML echoes represents the diastolic cleft of the AML. Review of the anatomy confirms this assumption

Transverse cardiac cross section with the echo-beam directed towards the aortic root normally shows approximation of the tip of the anterior tricuspid valve echo to the medial end of the IVS during systole separating from it during diastole Normal septal aorticcontinuity can also be observed at

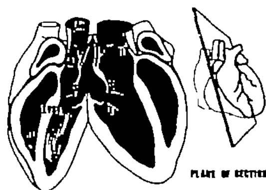


Fig 5 Anatomic drawing illustrating the abnormal mitral valve in AVC (i e atrial septal defect of the primum type) in a sagittal cross-section The anterior leaflet is divided into a superior (S) and inferior (I) segment The left ventricular outflow tract is narrow and elongated due to the anterior displacement of the AML N B Note that in this plane of section the posterior mitral leaflet is not reached R = right coronary aortic cusp L = left coronary aortic cusp

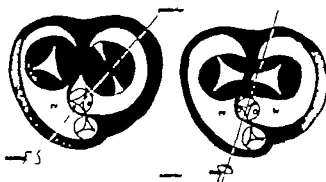


Fig 6 Diagrammatic sketch showing the position of the atrioventricular valves in normal subjects and in AVC (horizontal view) In AVC the cleft anterior mitral leaflet is positioned perpendicular to the interventricular septum rather than parallel to it as is normally the case In order to visualize this cleft AML a rather vertical plane of section was used In this plane of section the posterior mitral leaflet (PML) is not visualised

racteri tic however was the appearance of a break of AML echoes in diastole presumably representing the cleft of the AML (fig 3) It was formed by the lower part of the superior segment of the AML moving upwards and anterior into the LVOT while the inferior segment moved into an opposite direction downwards and posterior towards the left ventricular posterior wall The abnormal motion pattern and the diastolic cleft of the AML were best seen with the transducer in a rather vertical position due to the displacement of the AML in these patients The posterior mitral leaflet (PML) was usually not visualized in this plane of section Diastolic septal apposition of the AML was observed in all cases

In complete AVC the AML can be visualized crossing the IVS during diastole and appearing in the right ventricular cavity (S)

TRANSVERSE CROSS SECTION

The major findings in the transverse cross section at the level of the aortic root are the detection of the systolic alignment of the tricuspid and AML echoes in AVC malformation and the presence of an echo-free space in patients with complete AVC (group III) (fig 4)

PRELIMINARY EXPERIENCES IN 1 - AND 2 - DIMENSIONAL CONTRAST ECHOCARDIOGRAPHY

K D MÜLLER F GLET J STEINBAUER AND K BÜHLMEYER

From German Cardiac Center Munich Department of Pediatric Cardiology

Gramiak (5 6) and Feigenbaum (4) introduced the contrast echocardiography which primarily was used for identification of intra and extracardiac structures Two years ago we applied this technique for identification of the excessive superior-inferior movement and wall contraction of the RVOT in children with large LRS at atrial level by 2-dimensional contrast echocardiography At this time we injected isotonic saline solutions in a central venous catheter during routine cardiac catheterization

During the last few years contrast echocardiography has been extended to the evaluation of blood flow patterns in patients with RLS and LRS at different levels and valvular incompetence utilizing central and recently peripheral venous injections (1 3 7 12 17)
Using this technique echo-producing agents were injected into the bloodstream and resultant echo clouds were recorded by standard echocardiographic techniques simultaneously Explanations for the contrast phenomenon are temperature differences turbulence acoustic impedance differences and miniature bubbles due to a drop in pressure (2 4 8)

We investigated 12 children aged 11 days to 12 1/2 years mean age 3 years during routine cardiac catherization or in the early postoperative periode (table 1)

(Echo-cardio-Visor Organon Teknika)

ABBREVIATIONS:

[illegible]
[illegible] *right ventricular outflow tract*
[illegible] *left ventricular outflow tract*
[illegible] *left atrium*
[illegible] *right ventricle*
[illegible] *left ventricle*
[illegible] *right to left shunting*
[illegible] *left to right shunting*
[illegible] *right to left shunting at atrial level*
right to left shunting at ventricular level
no right to left shunting

this level In patients with AVC-malformation normal mitral-tricuspid dis continuity at this level is replaced by mitral-tricuspid alignment due to absence of the atrioventricular septum in these patients (7)

In this study two dimensional echocardiography proved much easier to perfrom and much less time-consuming than M-mode scanning especially in young chil dren and patients with Down s syndrome

CONCLUSION

Two-dimensional multiple crystal echocardiography shows a characteristic motion pattern of the AML in patients with AVC malformation Review of the anatomy suggests that this feature represents the cleft anterior mitral leaf let Due to the abnormal position of the AML perpendicular to the interven tricular septum its abnormal motion pattern is best visualized when the echo beam is adjusted accordingly

Continuously focussed multiscan provides better information than the technique used so far because of the improved lateral resolution over the entire field of view This had enabled us to visualize the cleft AML distinctly in all our patients and to diagnose AVC-malformation echocardiographically Visualiza tion of a ventricular septal defect and size and shape of the left ventricu-lar outflow tract give us some impression of the severity of the anomaly

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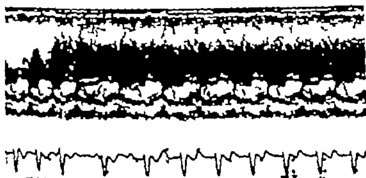


Fig 2.

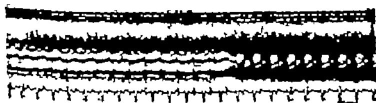


Fig 3

As echoproducing agents we tested dextrose in different concentrations phy siologic saline solution patients own blood and different human albumin solutions We injected 3 ml in newborns and babies and 5 ml in older children, which was forthfully done by hand So far we have no experiences with indocyanine green dye

During the investigation the patients were supine and tracings were recorded from position I and III similar to Feigenbaum s (fig 1) Position I means dissection of the aortic root LA and RVOT position III mitral valve level its orifice and LVOT

We found a similar quality of contrast patterns after peripheral as well as central injections

Isotonic saline- or dextrose solutions gave a better contrast than injections with the patients own blood or human albumine

In 6 cases we did not find any RLS in 4 RLS at atrial level one apparently through a defect interatrial patch and in other 3 children at ventricular level So far in 4 cases the RLS demonstrated by echo techniques were documented angiocardiographically In one case atrial and ventricular RLS could be demonstrated In a patient with Ebstein s anomaly after Hardy s plastic and closure of the atrial septal defect at the second postopera

Table 1

1	GI	8 10 75	Laevocardia situs inv. abd. single ventricle PA	+ A
2	HH	3 2 75	Fallot p Op	–
3	RH	221275	D-TGA Mustard-Brom Op	+ A
4	MR	3 4 73	ASD (Sinus venosus) p Op	–
5	GW	101072	Fallot p Op	+ V
6	DW	11 2 77	ASD I TI MI, CoA	–
7	SN	6 11 72	TA BT LK.	+ A
8	RR	22477	TGA+VSD	+ V
9	FM	21377	Ebstein anomaly	+ A
10	WM	9 872	Fallot	+ V
11	WT	26864	Ebstein anomaly Hardy Plastic	–
12	EW	15477	pred. CoA VSD (+PA Banding)	–

We injected different solutions peripherally into the antecubital hand foot or neck veins but also centrally into the right atrium vena cava superior and inferior In 3 cases investigated in the cath Laboratory we injected through angiocardiographic catheters and recorded the 1-dimensional** and observed or filmed the 2 dimensional cross sectional picture In 9 children investigated in the intensive care unit we used teflon catheters or needles

** (Echo K Siemens)

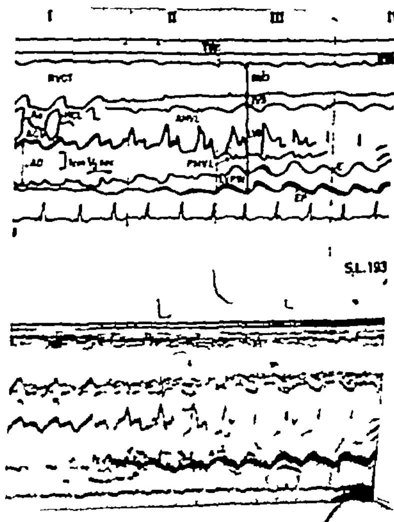


Fig 1



Fig 2

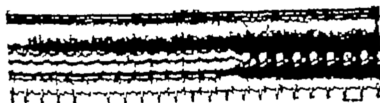


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TABLE I

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4	MR	3 4 73	ASD (Sinus venosus) p Op	-
5	GW	101072	Fallot p Op	+ V
6	DW	11 2 77	ASD I TI MI CoA	-
7	SN	6 11 72	TA BT LK.	+ A
8	RR	22477	TGA + VSD	+ V
9	FM	21377	Ebstein anomaly	+ A
10	WM	9 8 72	Fallot	+ V
11	WT	26864	Ebstein anomaly Hardy Plastic	-
12	EW	15477	pred. CoA VSD (+PA Banding)	-

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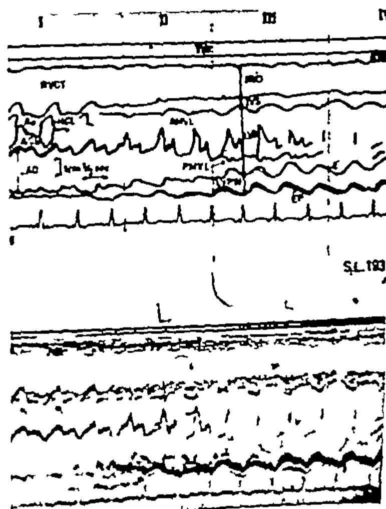


Fig 1

3 children demonstrated RLS at ventricular level In a child after repair of Fallot s tetralogy in position III the contrast clouds opacified the LV via LVOT rather than through the mitral valve orifice which remains echo-free in each diastole because non-opacified blood passes the valve The ultrasonic reflections reached the LVOT while the mitral valve was closed In this flow pattern echoes first appeared in the RV cavity during ventricular diastole During the following systole echoes were seen in the LVOT early in diastole of the following cardiac cycle during the isovolumic relaxation phase

In position I the clouds were limited to the aortic root while the LA was not filled The opacification appears first in the RVOT during late ventricular diastole and then in the aortic root during subsequent systole

In a 12 days old child with TGA and interatrial and interventricular RLS we found the combination of both flow patterns simultaneously (fig 4 and 5)

The timing of echo contrast flow patterns at atrial or ventricular level are in agreement with the excellent angiocardiographic analysis by Levin in 1966 to 1968 (9 11) According to his investigations blood crosses the intraatrial septum in RLS during rapid filling phase of ventricular diastole as well as the onset of LV contraction

Concerning interventricular shunts blood crosses from right to left at the onset of isovolumic relaxation when the LV pressure falls more rapidly than RV pressure In patients with equal systolic ventricular pressures Levin found RLS during late ventricular ejection as well as during isovolumic relaxation.

In shunts at atrial and ventricular level Valdes-Cruz (16 17) and Seward (15) described patterns of equal mitral as well as LV density in patients with larger atrial than ventricular shunts whereas that of scattered mitral opacification is obtained in patients with major ventricular shunting

In summary peripheral contrast echocardiography can be used as a sensitive test for more accurate diagnosis of RLS in different cardiac lesions in ambulatory patients Postoperative RLS can easily be evaluated by central



Fig 4

tive day dense clouds of echoes persisted longer due to low output state (fig 2 and 3) The contrast material - in this case 5 ml dextrose persisted for 46 cardiac cycles in the right sided heart (fig 2) In this case no intracardiac shunting could be found so the contrast echoes will be confined to the right ventricular cavity its outflow tract and the pulmonary orifice while the left sided structures remained echofree (fig 2 and 3)

In the 3 cases with RLS at atrial level we saw contrast echoes in the LA first normally during ventricular systole then in the RVOT during late diastole followed by the aortic root during subsequent systole (fig 4) In position III the most important diagnostic feature was the opacification of mitral valve orifice during diastole followed by the LVOT The echoes filled the RV cavity during ventricular diastole nearly simultaneously to the LV through the mitral valve funnel The LV filling can be delayed by one cardiac cycle



Fig 5

15 SHUB C TAJIK A J and SEWARD J B Detecting intrapulmonary right to-left shunts with contrast echocardiography observations in a patient with diffuse pulmonary arteriovenous fistulas Mayo Clin Proc 51 81 1976

16 VALDES-CRUZ L M PIERONI D R ROLAND J M ,A and SHEMATEK J P Recognition of residual postoperative shunts by contrast echocardiographic techniques (abstr) Am J Cardiol 37 178 1976

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contrast echocardiography Both techniques can detect and localize RLS at atrial and/or ventricular level The combination of routinely performed 1- and 2-dimensional echocardiography with ultrasound contrast techniques is safe reliable and an aid in the diagnostic assessment *of children with* cyanotic cardiac lesions

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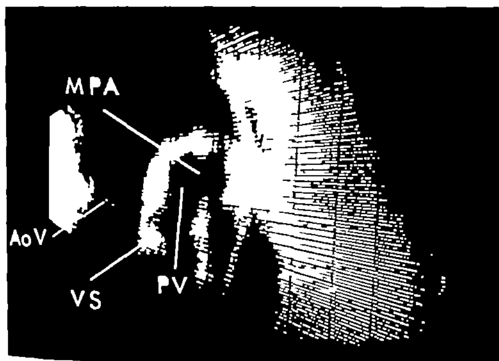


Fig 1 Longitidunal scan infant with TGA
VS ventricular septum. AoV = aortic valve PV – pulmonary valve
MPA main pulmonary artery

ECHOCARDIOGRAPHIC IDENTIFICATION OF THE AORTA AND PULMONARY ARTERY IN TRANSPOSITION OF THE GREAT ARTERIES

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From Royal Hospital for Sick Children and Department of Clinical Physics and Bio-engineering Glasgow

The echocardiographic diagnosis of transposition of the great arteries (TGA) has come to depend on the demonstration of an abnormal relationship between the great arteries no reliable echocardiographic technique has emerged for the separate identification of the aorta and main pulmonary artery (MPA) A mechanical 60^0 sector scanner providing a two dimensional echocardiogram has now been used to identify both great arteries in 14 children up to the age of 20 months (including five within the neonatal period) with complete TGA and two infants with primitive ventricle and TGA In a longitudinal scan the pulmonary artery is characterised by its posteriorly directed course immediately beyond the pulmonary valve and the aorta by its retrosternal course upwards before arching posteriorly Two-dimensional transverse scans demonstrate the exact spatial relation ship of the great arteries With this wide angle scanner a firm diagnosis of TGA may be achived in as little as one minute The MPA can also be identified by M-mode echocardigraphy alone upwards angulation of the transducer from the pulmonary valve demonstrates apparent widening of the vessel corresponding to the posteriorly directed course of the MPA The accurate assessment of great artery relationships and the positive identification of both great arteries will facilitate the echocardiographic diagnosis of other and more complex anomalies of the ventricu lar outlets

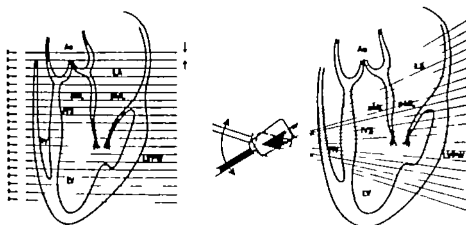


Fig 1 Schematic drawings of a longitudinal cross-section of the heart along the long-axis of the left ventricle together with indication of ultrasonic beams from the twenty elements of a multi-element transducer (left) and ultrasonic beams from an ordinary transducer used during M-mode scanning (right) The two vertical arrows in the left part of the figure points to the distance between two adjacent transducers in the multi-element transducer

MULTI-ELEMENT AUTOMATIC SEQUENTIAL LINE-SELECTION

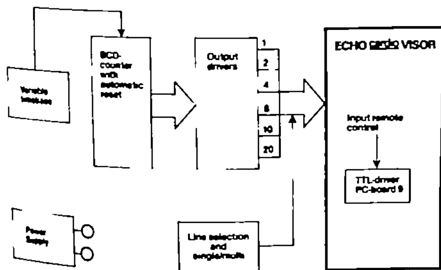


Fig 2 Block-diagram of the device used for automatic sequential line selection. BCD-counter - Binary Coded Decimal counter

In order to make such an investigation easier a simple device was constructed that enables this sequential line selection to be made automatically at

SINGLE-ELEMENT ECHOCARDIO-TOMOGRAPHY BY MULTI-ELEMENT AUTOMATIC SEQUENTIAL LINE-SELECTION

N -R LUNDSTRÖM AND R HANSSON

From the Department of Pediatric Cardiology University Hospital Lund Sweden

In echocardiography using the single-element technique M-mode scanning plays an important role M-mode scanning means as is well known that a continuous recording is made while the direction of the transducer is changed By this method it is possible using a single ultrasonic beam to demonstrate relations and connections between different intracardiac structures It is therefore not surprising that this method has been used very often in pediatric cardiology and in evaluation of complex congenital malformations of the heart This method can provide some sort of two-dimensional impression of cardiac structures There is however some drawbacks of the method The final resulting M-mode scan is to a large extent depending upon the speed of the scanning manoeuvre and this can hardly be standardized The M-mode scan therefore does not allow measurements of distances along the scanning axis The scanning will cover a triangular area (Fig 1) This will however be displayed in rectangular form resulting in distorsion of the geometric shape especially of the anterior structures

The M-mode scanning thus seems unsuitable for demonstration of geometric shape Such information is of course available by two dimensional echocardiography (Fig 1) So far the resolution of the two-dimensional echocardiographic recordings has however not been comparable to that of M-mode echocardiography

In two-dimensional echocardiography using the multi element system (Bom et al 1973) a single-element M-mode echocardiogram can be obtained along any of the twenty lines used in this system By making short single-element M-mode echocardiograms along all these lines starting with line no 1 and ending with line 20 a sort of two-dimensional picture can be obtained and particularly a picture that shows the various intracardiac structures with a more true demonstration of geometric form and shape By doing this manually it is however difficult to avoid changing the position of the transducer during the examination and thereby making this examination of less interest

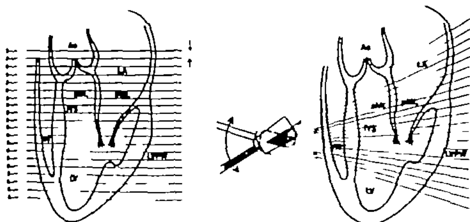


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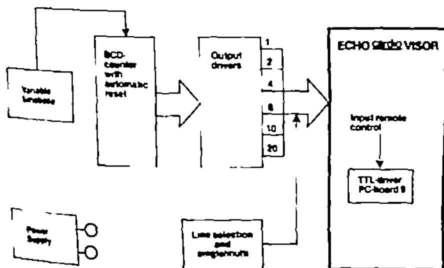


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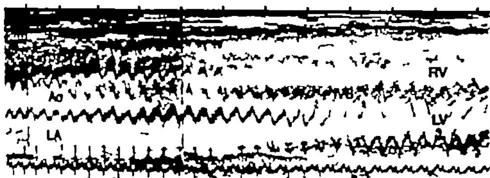


Fig 5 Echocardiogram obtained by single-element echocardio-tomography with the transducer placed along the long-axis of the heart in a patient with Fallot s anomaly The wide aortic root (Ao) can be seen to over-ride the interventricular septum (IVS) separating the right ventricle (RV) from the left ventricle (LV) The echocardiogram obtained with the same transducer as Fig 3

any desired speed (Fig 2) The main part of this device is an automatic Binary Coded Decimal counter with automatic reset and galvanically isolated output drivers This automatic BCD-counter has a time base that can be varied as desired This small device has been built in a separate unit with separate power supply and connected to the multi-element echocardiographic equipment without any modification on this unit

The multi-element 2 25 and 4 5 MHz transducers have a length of 80 mm and 7 MHz transducer a length of 50 mm which means that the distance between two adjacent single-element lines is 4 and 2 5 mm s respectively (Fig 1)

Fig 3 shows a recording made with this equipment with the transducer placed along the long-axis of the left ventricle With the transducer placed along the outflow tract of the right ventricle it can clearly be seen that the outflow tract of the right ventricle and the pulmonary artery is deviating in posterior direction (Fig 4)

In another recording made with this equipment on a patient with Fallot s anomaly the overriding of the wide aorta can clearly be demonstrated (Fig 5)

We have used this system in routine work in more than 50 patients Echocardiograms of a quality like those shown in Figs 3 5 have been obtained in more than 90% of the patients The main problem encountered has been to find a proper gain and reject setting suitable for all the recording levels



Fig 3 Echocardiogram obtained by single-element echocardio-tomography with the transducer placed along the long-axis of the left ventricle showing the normal relation between the aortic root (Ao) and the left ventricle (LV) The small markings on top of the recording shows the border between the single-element echocardiogram obtained with each individual transducer of the multi-element transducer With the 5 MHz transducer used in this recording the distance between the levels from which two adjacent M-mode recordings are obtained is 4 mm

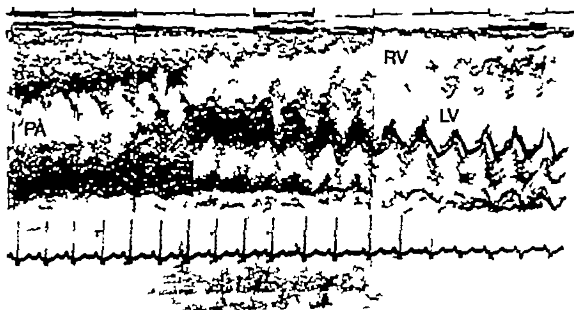


Fig 4 Echocardiogram obtained by single-element echocardio-tomography with the transducer placed along the outflow tract of the right ventricle The posterior deviation of the outflow tract of the right ventricle (RV) and the pulmonary artery (PA) is demonstrated. The echocardiogram obtained with the same transducer as Fig 3

ECHOCARDIOGRAPHIC FINDINGS IN CARDIAC TAMPONADE

K J HAGEL

From the Department of Pediatric Cardiology (Prof Dr Rautenberg) Center of Pediatrics University of Giessen German Federal Republic

The echocardiographic findings of two pediatric patients (6 and 13year-old) with clinical evidence of cardiac tamponade are demonstrated The recordings were made immediately before and after pericardial drainage The most diagnostic finding for cardiac tamponade in both cases was a reduction of the mitral E-F slope due to a decreased diastolic compliance of the heart with impaired left ventricular filling The abnormal motion of the pulmonary valve diminished aortic wall movement and periodic changes of the ventricular diameters are demonstrated and discussed

In 1955 Edler (2) was the first to use ultrasound in the diagnosis of pericardial effusion Feigenbaum (3) drew attention to this method in 1965 showing the clinical usefulness and accuracy ot the new diagnostic procedure Most following reports deal with technical comments of detecting the pericardial effusion and with its quantitative assessment (4 6) Till now only few investigators looked for a possibility to ascertain the dramatic complication of pericardial effusion cardiac tamponade with ultrasound (1 5)

Therefore we want to demonstrate in the following the echocardiographic findings in two pediatric cases of cardiac tamponade The investigations were performed on an Echocardiovisor connected to a stripchart Honeywell recorder 4 5 and 5 0 MHz unfocused transducers with an outer diameter of 0 5 cm and 1 0 cm were used

In both children the investigation was quite difficult because they showed marked dyspnoea and were very anxious so they could not lie quiet for a longer period in standard supine position The echocardiograms were recorded just before pericardial puncture or pericardiectomy and immediately afterwards

Case 1 Ch. H a 13-year-old girl Three weeks before admission she felt ill with fatigue fever and seldom vomiting On admission the girl showed respi

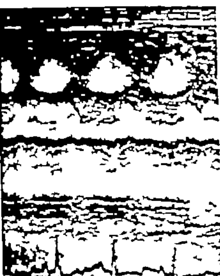
A change of the reject control is however possible during the recording

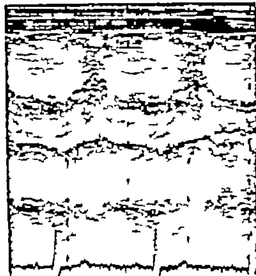
A further improvement in resolution could be obtained by a pre set pattern of time-gain compensation for each line used Such an arrangement would also improve the resolution in the two-dimensional picture

Since these recordings are made by single element M-mode technique in sequential levels along a multi element transducer we have called it single-element echocardio tomography or ECT

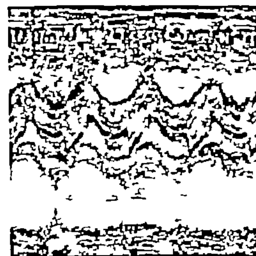
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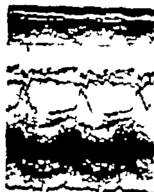
A B

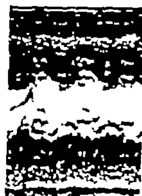
F 3 -- Aortic wall movement with improvement after pericardiocentesis (B)

In cardiac tamponade the diastolic echos of the pulmonary valve was almost horizontal and no a-wave could be detected (Fig 3 A) After decompression of the heart there was a constant a-wave of about 5 mm (Fig 3 B)

The only echocardiographic finding that did not change after drainage of the pericardium was the normal movement of the tricuspid valve (Fig 4)

Case 2 A. Sch a 6 year-old boy Two weeks before admission in our hospital he had first signs of chickenpox with a normal course in the beginning

A B C

Fig 1 A Both cases in cardiac tamponade with a large pericardial effusion anterior and posterior of the heart The EF-slope of the mitral valve is reduced B After decompression of the heart the EF-slope is normal in both cases although in case 2 there is still a large effusion

ratory distress hepatomegaly and elevated jugular venous pressure The ECG was normal except a relative low voltage There was no electrical and mechanical alternans The chest roentgenogram showed an enlargement on both sides of the cardiac silhouette The now performed echocardiogram revealed a large pericardial effusion anterior and posterior of the heart (Fig 1 A)

The anterior mitral valve showed a clear reduction in the early diastolic closing movement The posterior mitral valve moved opposite like normal In systole a prolapse pattern of both mitral valves was recorded (Fig 1 A)

The puncture of the pericardium was performed and we removed about 800 ml of a sero sanguineous fluid The echocardiogram of the mitral valve movement was now normal with normal E F slope (Fig 1 B) Both right and left ventricular enddiastolic diameters were still enlarged

In Fig 2 before drainage of the pericardium the aortic wall movement was reduced and showed a slight improvement afterwards





Case 1 Case 2

Fig 4 Tricuspid valve movement with normal E-slope before and after drainage of the pericardial effusion.

mitral valve was decreased The posterior mitral valve moved backwards In contrast to case 1 we saw here periodic changes in the diameter of the right and left ventricle (Fig 1 A)

After puncture of the pericardium with removal of 350 ml fibrinous fluid the boy was soon in a much better general condition with only mild respiratory distress

In the afterwards performed echocardiographic recording the E-F slope of the mitral valve was normal although a large amount of pericardial fluid anterior and posterior of the heart was still present (Fig 1 B)

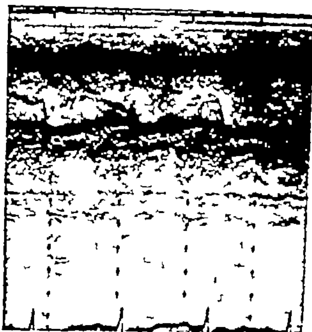
When pericardiectomy had been performed with removal of about 500 ml of a serosanguinous fluid the echocardiogram immediately afterwards showed an identical normal E F slope (Fig 1 C)

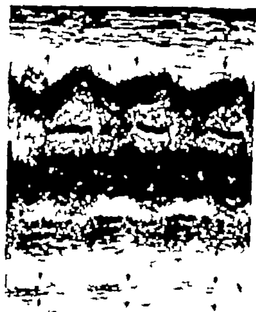
In addition to these mitral findings there were almost the same changes in the aortic wall movement and the echoes of the pulmonic valve before and after the pericardial drainage as described in case 1

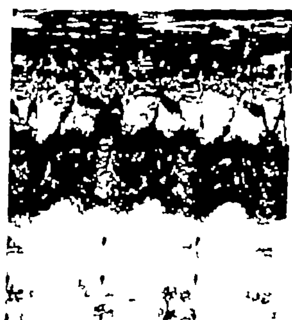
Identical to case 1 the pulmonary valve is recorded with an almost horizontal E F slope and a nearly absent a-wave (Fig 3 A) After decompression of the heart the a wave is 7 mm deep (Fig 3 B)

The unchanged normal motion pattern of the tricuspid valve is also recorded (Fig 4)









A B

Fig 3 A Pulmonic valve recording in cardiac tamponade with almost absent a-wave B After decompression of the heart the a-wave is 5 mm in case 1 and 7 mm in case 2

10 days later the boy was in bad general condition with fever and cardiac malfunction The chest roentgenogram in a outside clinic showed an extremely enlarged cardiac silhouette On admission he was ortopnoeic with ascites hepatomegaly and raised jugular venous pressure The ECG was without abnormalities except low voltage

The echocardiographic examination revealed a large pericardial effusion an anterior and posterior of the heart Similar to case 1 the E F slope of the

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We demonstrated these two pediatric cases because we believe that these fin dings may be helpful in the diagnosis of cardiac tamponade The most remarkable finding seems to be the reduction of the E-F slope of the mitral val ve in both cases similar to 3 cases of cardiac tamponade of D CRUZ (1) due to a decreased diastolic compliance of the left heart with impaired left ventricular filling as QUINONES (8) reported in connection with other car diac diseases He found a good correlation between the mitral valve slope and the enddiastolic distensibility index In cardiac tamponade this index is reduced and therefore also the E F slope of the mitral valve NANDA and GRAMIAK (7) lately demonstrated abnormal motions of cardiac valves and other structures in large pericardial effusion which all normalises after removal of the pericardial fluid They claim that there should be no diagnostic and therapeutic conclusion out of these abnormal findings In case 2 we could demonstrate that there was a significant acceleration of the mitral valve E F slope after only partial removal of the pericardial fluid We therefore think that this constant finding of the E-F slope is a diagnostic hint for cardiac tamponade

The pulmonary valve tracings in cardiac tamponade in case 1 and 2 are diag nostic signs of pulmonary hypertension secondary to pulmonary venous ob struction

The shown diminished aortic wall movement does not seem to be a good indicator for low cardiac output

D CRUZ (1) tried to show in 3 cases of cardiac tamponade that with paradoxical pulse during inspiration left ventricular filling and stroke volume decreases Only in our case 2 similar periodic changes in the left ventricular diameters were recorded but without registration of respiration Measurement of vent ricular size seems to be very difficult when the heart like in cardiac tamponade is in no constant position but is swinging in the fluid filled pericardium We therefore do not believe that reproducable measurements of the ventricular diameters is possible

In conclusion we hope that our findings in addition to reports of others will help to find a proven way in the echocardiographic diagnosis of cardiac tamponade

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ECHOCARDIOGRAPHIC FINDINGS IN VENTRICULAR SEPTAL RUPTURE AND ANTERIOR WALL ANEURYSM COMPLICATING MYOCARDIAL INFARCTION

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ABSTRACT

Echocardiographic findings in a patient with ventricular septal rupture and anterolateral wall aneurysm complicating myocardia infarction are presented The findings were confirmed by cardiac catheterization and surgery Using M-mode ultrasonocardiography one was able to demonstrate and localize the aneurysm as well as the ventricular septal defect which presented as an oblique interventricular communication appearing only during systole Thus echocardiography supplemented the invasive examinations in exactly revealing the site of ventricular septal rupture Other echocardiographic features of ventricular septal rupture were right ventricular dilatation pathological septal motion and abnormal tricuspi valve motion as recently reported by other authors

Ventricular septal rupture (VSR) is a rare complication of acute myocardial infarction (0 5 1 %)(5) VSR is presented by the sudden occurence of a systolic murmur accompanied by clinical deterioration There is a common association with left ventricular aneurysms and the prognosis is grave (5) Since surgical correction i not infrequentlyfeasible accurate diagnosis is important Cardiac catheterisation and selective coronary arteriography are generally required As presented in this paper echocardiography too provides valuable informations

CASE STORY

A 48 year old woman was admitted to hospital with an anterior transmyocardial infarction Except for treated hypertension and a present RBBB there was no previous history of cardiovascular disease Four hours after admission the condition abruptly aggravated Severe hypotension occured and simultaneously a loud systolic murmur was noticed The patient did not succomb to the acute exacerbation but she recovered only slowly and though treated with digoxin

ed diuretics she was persistently characterized by cardiac failure on very little effort Subsequently five months after the acute infarction the patient was transferred to the department of cardiology Copenhagen County Hospital Gentofte

Clinical examination revealed no signs of cardiac failure at rest The blood pressure however was 110/80 and the pulse rate 100 Abnormal systolic pulsation and a thrill was felt outside the midclavicular line A grade 5/6 holosystolic harsh murmur with maximum at the apex and the lower left sternal border radiating to the axilla was heard ECG revealed sinus rhythm right bundle branch block (RBBB) and anterior infarction with persistent S-T segment elevations Chest X ray demonstrated cardiomegaly and a large bulge at the left contour of the heart

ECHOCARDIOGRAPHIC FINDINGS

Echocardiograms were performed using SKI Ekoline 20 ultrasonic apparatus connected to a Tektronix oscilloscope The ultrasonic frequency was 2 5 MHz and the transducer focused at 10 cm M-mode recordings were obtained on Polaroid[R] prints using open shutter technique The patient was examined in the supine position

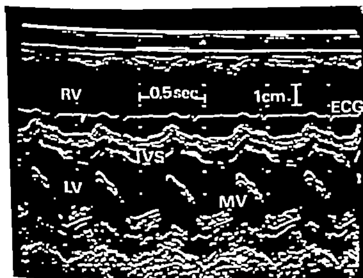


Fig 1 Echocardiogram obtained from the left fourth intercostal space at the sternal border The recording demonstrat right ventricular dilatation while the left ventricle is not dilated The interventricular septum is almost akinetic during systole and exhibits in diastole a diphasic motion pattern which to an extent resembles the echocardiogram of the anterior mitral cusp RV right ventricle LV left ventricle IVS interventricular septum MV mitral valve ECG electrocardiogram

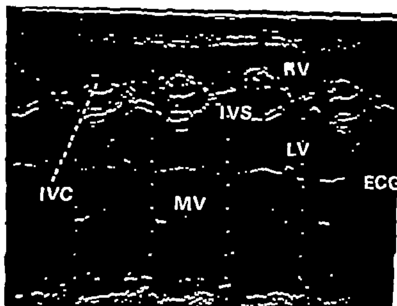


Fig 2 M-mode recording obtained from the left fifth intercostal space in the midclavicular line During systole the interventricular septum (IVS) is splitted into two layers separated by an echofree zone which represents an obliquely passing communication (IVC) connecting the left (LV) to the right ventricle (RV) MV fragments of the anterior mitral leaflet ECG electrocardiogram Same units as in fig 1

Fig 1 is obtained from the left fourth intercostal space at the sternal border The echocardiogram primarily demonstrates right ventricular dilatation while the left ventricle in this diameter near the basis of the ventricle not exceeds normal values (6) The recording of the interventricular septum shows in diastole a diphasic pattern with a certain resemblance to an M-mode recording of the anterior mitral leaflet During systole the septum is almost a kinetic and the systolic thickening is severely reduced The mitral valve echocardiogram is essentially normal

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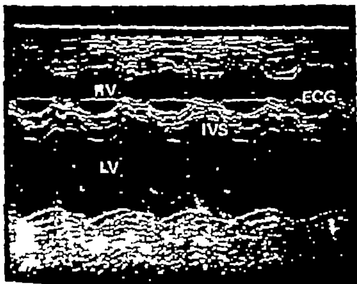


Fig 8 Echocardiogram obtained from the left sixth intercostal space two cm lateral to the midclavicular line The recording illustrates paradoxical motion of the anterior wall of the right ventricle Septal motion as demonstrated in fig 1 RV right ventricle LV left ventricle IVS interventricular septum ECG electrocardiogram Same unit as in fig 1

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A pulmonary hypertension (58/26 mm Hg) and a left to right shunt of 3 1 at the ventricular level was found Left ventricular angiocardiograms revealed in right anterior oblique position a large anterolaterally located aneurysm but no regurgitation to the left atrium Left anterior oblique angiocardiograms proved simultaneous contrast filling of the conus of the right ventric le The exact position of the shunt however was impossible to define Coronary arteriography a m Judkins demonstrated subtotal occlusion of the left anterior descending branch of the left coronary artery 4 cm distal to the bif rcation Other coronary artery branches were all normal At surgery an aneurysm measuring 8 cm in diameter and involving the antero lateral wall of the heart was removed Four slit like ruptures each measu ing approximately 0 8 cm along the major axis and located in the upper part of a fibrously degenerated muscular septum were repaired No reconstructive coronary artery s rgery was required

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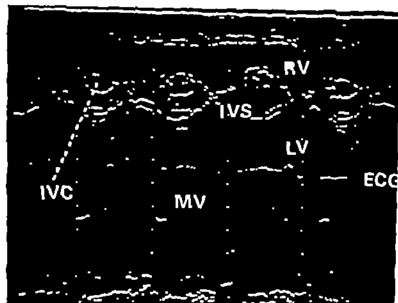


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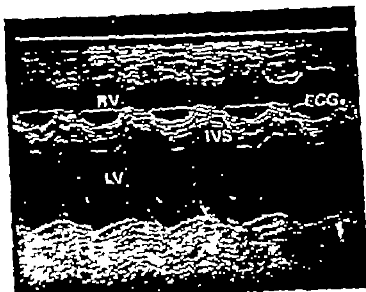


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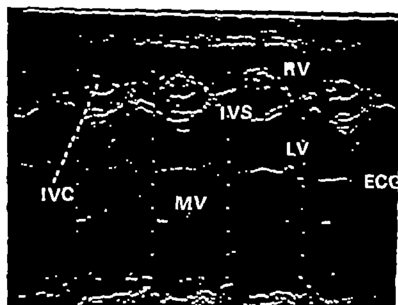


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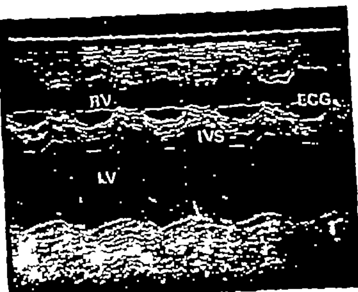


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DISCUSSION

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papillary muscle injury As stated by Dugall et al (5) the clinical differentiation is unreliable Until recently cardiac catheterization and angiography were the only methods for obtaining the exact diagnosis Echocardiography however represents an alternative way of establishing the nature of the cardiac catastrophic event Furthermore informations concerning the feasibility for surgical repair are obtained using ultrasound examination Chandraratna et al (3) established right ventricular dilatation as the most salient echocardiographic feature of VSR Silverman et al however was unable to demonstrate right ventricular dilatation in one of three patients examined within few hours of ventricular septal rupture (9) Abnormal septal motion in VSR has been reported by De Joseph et al (4) and Silverman et al (9) who also demonstrated diminished or reversed EF slope of the tricuspid valve echocardiogram The non specific echocardiographic features of mitral insufficiency are augmented septal motion amplitude and dilatation of the left ventricle and atrium (2 6) Rupture as well as dysfunction of the chordae and papillary muscle apparatus are claimed to produce characteristic alterations of the mitral leaflet motion patterns (2 6) These pathological findings are however not always present (8)

In the case presented echocardiographic examination revealed right ventricular dilatation while none of the signs of mitral incompetence were recorded Furthermore the septum demonstrated not only systolic hypokinesis and subnormal thickening but also an abnormal diastolic motion pattern which was taken to account of pronounced septal fibrosis and resulting passivity to the diastolic filling of the left ventricle (RBBB does not change the motion pattern of the interventricular septum (1))

The interventricular communication demonstrated was easy to reproduce The possibility of recording a ventricular septal defect even with careful examination is however unpredictable Two-dimensional realtime scanning or pulsating Doppler-examination may prove useful According to Feigenbaum et al (7) a normal size of the basis of the left ventricle indicates a not disadvantageous prognosis of aneurysmectomy Normal contractility of the non infarcted myocardium also demonstrated is as well important evaluating the patient for surgery (7) Thus these findings may be essential in selecting patients for further investigative and surgical procedures

In the present case left ventricular angiocardiography demonstrated a superiorly located ventricular septal defect but was unable to point out the exact site of the shunt Considering the RBBB which has been diagnosed prior to the infarction it was impossible to exclude a congenital defect

(Informations of earlier heart auscultation were not available) The opera tion however finally confirmed the echocardiographic diagnosis of rupture in the upper muscular part of a firmly scarred ventricular septum

In summary echocardiography seems very suitable in diagnosed cardiac complications of acute myocardial infarction In the case presented an anterolateral aneurysm and a ventricular septal rupture were revealed Heart catheterization with selective coronary arteriography are generally required in the final evaluation for surgery In the present case however echocardiography supplemented the invasive examinations in precisely loca ting a ventricular septal rupture

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QUANTITATIVE ANALYSIS OF LEFT VENTRICULAR FILLING PHASE BY ECHOCARDIOGRAPHY

P BRUN C ODDOU (*) E BERALDO A KULAS F LAURENT
A PHILIPPON F DE VERNEJOUL

From the Groupe de Recherce U 138 de l I N S E R M Service d Exploration Fonctionelle C H U Henri Mondor Créteil France

ABSTRACT

The ultrasonic method was used in an attempt to correlate the different mechanical events occuring during left ventricular rapid filling phase concerning anterior mitral leaflet posterior wall and interventricular septal motions

Signals were recorded on a line scan recorder The M-mode records were placed on a digitizing tablet under the control of a mini-computer for continuous measurements throughout the cardiac cycle Q waves were indicated to identify end-diastole and heart rate The left ventricular internal diameter (minor axis) and its rate of change were calculated from anterior and posterior endocardial echos together with posterior wall and septal thickness external and mid-wall diameter The analysis was made on data obtained from 40 normal subjects

The results suggest that our echographic measurements of the left ventricular internal diameter rate of change and the electromagnetic transmitral flow time variation present a high temporal correlation:

1: Peak rate of change of the internal diameter lengthening and peak mitral flow occur shortly after the anterior mitral leaflet E wave (echographic data: 26 ± 30 ms)

2: In the case of long diastole rapid lengthening and filling phase ends before mitral F point (echographic data: 43 ± 37 ms)

The abrupt slope change of the posterior wall occuring during early diastole precedes significantly the end of rapid filling (50 ± 30 ms), which is indicated by an abrupt slope change of the interventricular septum

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The improved quality of time motion echocardiograms related to linescan recorders allows identification of posterior wall endocardial and epicardial echos and left and right septal endocardial echos and satisfactory mea surements of both myocardial thickness and internal diameters Routine mea surements concern end-diastole and end systole and a shortening ratio (often expressed as an ejection fraction) and a thickening ratio can be derived correctly correlated with cineangiographic estimates

So a continuous analysis of the rate of change of wall thickness and left ventricular dimensions has been proposed (1 2 4) Diastolic changes of short axis diameter are assumed to be related to ventricular filling properties although the left ventricle change of shape prevents satisfactory volume and flow calculations

The purpose of this work is to analyse simultaneously during diastole and mainly during its rapid filling phase a) the posterior wall and interventri cular septum echograms (including the study of the slope changes) b) the an terior mitral leaflet echogram c) the internal diameter rate of change Focus is directed toward the analysis of time relations between the different mecha nical events

METHODS AND MATERIAL

The device employed to record the echocardiograms was the Echocardiovisor (Organon Technika) which has conventional single element and multiscan capa bility M-mode signals were recorded on a Honeywell linescan recorder To record the diastolic motion of the anterior mitral leaflet the transducer was aimed toward its free edge and then slightly angulated so that on the same recording could appear septal and posterior wall echograms satisfying the requisites for left ventricular minor axis measurements The M-mode recordings were always preceded by a dynamic mode observation so that the results of improperly oriented left ventricle (long axis and echo beam angular relationship) could be rejected

The M-mode recording was placed on a digitizing tablet (Wang Digitizer resol tion 0 25 mm) and the selected echos were traced This was done under the control of a Wang 2200 Calculator (16 K-octets) with a floppy disk unit and a XY plotter (fig 1) The sampling rate was related to the recording speed (200 pe second for a 50 mm per second speed) The following structures were recorded a) the left and whenever possible right side of the interventricular septum b) the anterior mitral leaflet c) the endocardium and epicardium of the left ventricular posterior wall Each trace was submitted to three conse-

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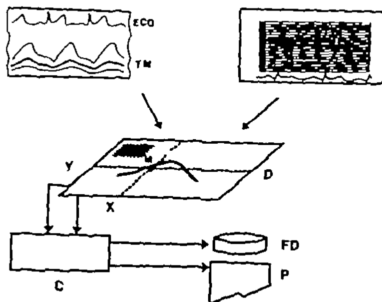


Fig 1 Diagram of the computer-assisted system for M-mode digitizing storage and display (M M-mode recording C Minicomputer FD Floppy disc unit P XY plotter)

cutive readings on the digitizing tablet and the averaged results corrected for scale were stocked on disks without any filtration A three points algorithm was used for differentiation

These data were computed to derive throughout the cardiac cycle a) the internal diameter (D 1) b) the external diameter (D 2) and the averaged mid wall diameter (D 3) c) the rate of change of these diameters d) the interventricular septal thickness, e) the posterior wall thickness f) a characteristic volume $W = (D\,2/2)^3 - (D\,1/2)^3$ related to the myocardial volume

Echocardiograms were obtained from 40 normal subjects 12 35 years old including trained athletes

RESULTS

An example of results is shown in fig 2 Top left the five traces are plotted corresponding to septal and posterior wall boundaries and to the anterior mitral leaflet All recordings are synchronized with the Q Wave of the electrocardiogram Bottom-left the septal and posterior wall thickness and the characteristic volume W are displayed Top-right the instantaneous left ventricular dimensions (external midwall internal diameters) and bottom-right their rate of change (midwall and internal diameters) are displayed The chronology of the different mechanical events are indicated by the broken lines the points D E F on the anterior mitral leaflet the change of slope noted I on the posterior wall the change of slope noted J on the interventricular septum peak lengthening velocity (internal diameter) noted X and its zero crossing Z The sequence D E X I J (Z) F is highly representative of the overall results

These results are summarized in tables I and II In table I the amplitude of different parameters are presented including the shortening diameter ratio the ejection fraction the thickening ratio the endocardial and midwall mean

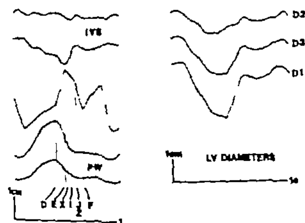
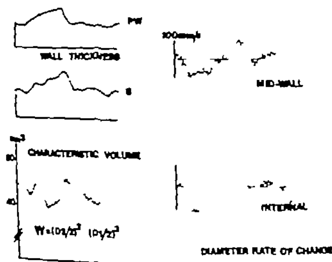
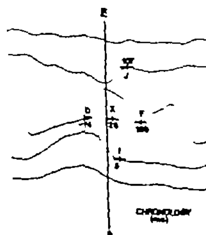


Fig 2: An example of digitised M-mode recordings of posterior wall interventricular septum anterior mitral leaflet and derived parameters (see text)-



circumferential fiber shortening rates values in good accordance with the echocardiographic standards and the mean posterior wall thickening rate in good accordance with recent angiographic results (3)

In table II the chronology of the statistically averaged results concerning the rapid filling phase is presented The results are expressed in two different ways a) referred to the Q wave of the electrocardiogram b) reffered to the E wave of the anterior mitral leaflet (fig 3)



The mitral point D occurs respectively at 426 4 ± 33 9 ms and 73 6 ± 19 3 ms the mitral E wave 500 0 ± 43 0 ms the diameter peak rate of change (point X) 525 9 ± 49 7 and 25 9 ± 30 4 ms the posterior wall abrupt slope change (point I) 556 6 ± 51 3 and 56 6±31 4 ms the septal abrupt

Fig 3: Schematic representation of the chronology of the statistically averaged results concerning the rapid filling phase referred to E wave (see text)

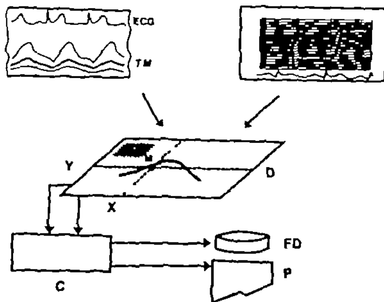


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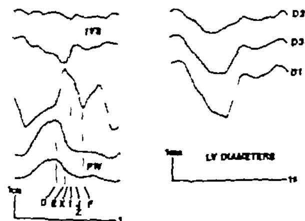
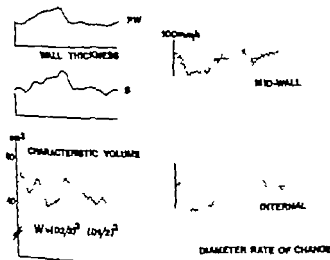
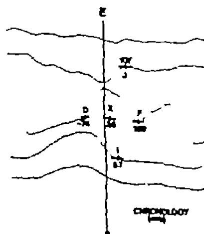


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TABLE I Amplitude results and derived parameters

LEFT VENTRICLE	
End diastolic diameter	47 3 ± 8 2 mm
End systolic diameter	33 2 ± 6 7 mm
Shortening ratio	29 + 07
Ejection fraction	67 + 08
POSTERIOR WALL	
End diastolic thickness	7 0 + 1 9 mm
End-systolic thickness	11 4 + 3 6 mm
Thickening ratio	1 67 ± 45
MEAN CIRCUMFERENTIAL FIBER SHORTENING RATE	
Endocardial	*1 51 circ/s*
Mid wall	73 circ/s
THICKENING RATE	
Posterior wall	1 95 thickness/s

TABLE II Chronology of the mechanical events occuring during the rapid filling phase (milliseconds)

REFERENCE	Q wave	E wave
Point D (anterior mitral leaflet)	426 4 + 33 9	73 6 + 19 3
Point E (anterior mitral leaflet)	500 0 + 43 0	
Point X (peak lengthening velocity)	525 8 + 49 7	25 9 ± 30 4
Point I (posterior wall)	556 6 + 51 3	56 6 + 31 4
Point J (interventricular septum)	606 6 + 43 6	106 6 ± 32 9
Point F (anterior mitral leaflet)	650 0 + 49 4	150 0 + 27 9

slope change (point J) 606 6 ± 3 6 and 106 6 + 32 9 ms the mitral point F 650 0 + 49 4 and 150 0 + 27 9 ms The end of rapid filling derived from the internal diameter can be evaluated only from long diastole Its occurence then derived from its rate of change zero-crossing Z is syncronous with J Occasionally the diameter then decreases until the point F

The pattern of the posterior wall thickness variations during the cardiac cycle is well known though its description during the filling phase remains poorly detailed We found a similar pattern for the interventricular pattern but with a slight asynchronism The three filling phases (rapid slow atrial contraction) are clearly demonstrated on the internal diameter curve In spite of the incompressibility of the myocardium the characteristic volume V showed a 10 % minimal scatter due to various factors discussed below

DISCUSSION

Cineangiographic studies demonstrate variable eccentricity of the left ventricle (variable axis ratio in an ellipsiodal or truncated ellipsoidal model) throughout cardiac cycle Mitral flow therefore cannot be derived from diastolic continuous diameter rate of change However if the rate of change of the axis ratio exhibit small temporal gradients internal ventricular volume and diameter time variations may be highly correlated

The successfull simultaneous recording of mitral flow and cusps motion in animal experiments has permitted to examine their dynamic relations (5)

Our findings locating peak velocity of short axis lengthening 25 9 + 30 4 after the echographic E wave are in good accordance with transmitral flow measurements and enhance the reliability of echographic measurements (no phase disturbance)

It is commonly admitted and found in most published examples of simultaneously recorded transmitral and anterior mitral leaflet echogram that flow is still positive at F point Our findings could lead to different conclusions If a sufficient diastolic duration is present diameter lengthening rate of change do cross zero line before (45 ms) F point and occasionally becomes negative at F point Indeed we were able to collect examples of transmitral flow with long diastoles and traces demonstrate zero flow around the echographic F point (5) Contradiction is therefore avoided It must not be concluded that effective mitral flow is null both transmitral flow and diameter variations referring to a total annular flow Our examples with short diastolic duration show positive diameter variations It is concluded ...

graphic internal left ventricular diameter and transmitral flow are highly correlated as long as time is considered

The abrupt slope change observed on the endocardial echo of the left ventricular posterior wall precedes significantly the end of the rapid filling phase (50 0 ± 29 6 ms) and F point (93 4 ± 32 8 ms) the diameter increase in its terminal phase is related to septal motion An abrupt change of slope is in turn observed on the septal echogram this time coinciding with the end of the rapid filling phase (43 4 ± 37 3 before F point) The significance of this echographic asynchronism of the left ventricular walls motion is not clear due either to ventricular motion as a whole or to local phenomenons

The opportunity to follow simultaneously the right side of the interventricular septum and the epicardial border of the posterior wall allows the computation of the left ventricular external diameter It seems interesting for physiological purposes to consider the averaged value of internal and external diameters defined as mid wall diameter in the site where the circumferential fibers are located anatomically (6)

The value of such computation depends on its entry date parameters the improved quality of the echocardiogram does not prevent ambiguity in path selection when a given boundary has to be read A first possible test consists in an analysis of the thickening and thinning patterns of myocardial walls which prevents major errors but a second test based on the myocardial volume constancy seems available and of greater interest This property is used with angiographic method to calculate the thickness variations of the left ventricular wall The inaccuracy of the end systolic wall thickness prevent a direct evaluation (computation of the myocardial volume with end systolic data would give a result with considerable excess in the expected value)

With echocardiography the wall thickness is measured with similar accuracy throughout the cardiac cycle To include the term myocardial volume constancy we have calculated the characteristic volume parameter $W = (D2/2)^3$ $(D1/2)^3$ Computation of left ventricular internal volume with angiography demonstrate a continual variation in the degree of ellipsoidal eccentricity related to the smaller variations of the long axis compared with the short axis W dependant of the axis ratio must show a significant (but of limited amplitude) end systolic decrease Observed variations are related to superimposition of these variations and reading errors concerning the selec

ted boundaries A continuous analysis of the axis ratio by cineangiographic method would contribute to the applicability and interest of the test

ACKNOWLEDGEMENTS

This work was supported by a grant from the Délégation Générale à la Recherche Scientifique et Technique (A C C Biologie et Fonction du Myocarde)

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Supplementum 628

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Edited by Lennart Hansson and Matts Henning

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In our opinion these aspects of blood pressure lowering therapy also require attention. Hence, we invited clinically oriented researchers to give brief summaries of the negative effects of blood pressure reduction as such, e.g. as regards the cerebral circulation, and also side effects from antihypertensive drugs affecting various organs or organ system. These presentations were given at a conference held on June 2nd 1978 in Foresta, Stockholm.

In order to balance the negative effects of blood pressure lowering treatment reported during the meeting against its undisputable beneficial effects of such therapy a panel discussion on the risk-benefit aspect concluded the meeting.

This supplement contains nearly all the presentations given as well as excerpts of the discussion and a summary of the panel discussion, the purpose being to make a compiled information available to a wider range of clinicians than those present at the conference.

As organizers of the conference and as editors of this supplement we wish to express our sincere gratitude to CIBA-GEIGY Pharmaceuticals Division of Sweden and Anders Lindqvist who made it possible to arrange the meeting and to publish the proceedings.

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NEGATIVE CONSEQUENCES OF BLOOD PRESSURE REDUCTION

Lennart Hansson

INTRODUCTION

The beneficial effects of blood pressure reduction in hypertensive patients have gained general acceptance during the last two or three decades mainly due to the fact that reduced morbidity and mortality can be demonstrated when such therapy is instituted (Veterans Administration 1967 Veterans Administration 1970 Berglund et al. 1978)

It is also well known that all forms of pharmacological treatment will cause not only the therapeutic effect but also adverse effects (Netter 1976).

Regarding the balance between the therapeutic effect and the adverse effects it is also quite obvious that the safety of any particular compound has to be related to the efficacy of the drug, to the seriousness of the disease to be treated and to other available therapies (Liljestrand 1976)

In consequence, this benefit-risk ratio would not be constant for any certain drug but will vary with time. Since the purpose of this symposium is to evaluate the benefit-risk ratio for antihypertensive therapy with a strong emphasis on the risk side, a list of possible effects of drug treatment is given in Table I.

The definition of a side effect as been given as any response to a drug that is noxious and unintended and that occurs at doses used in man for prophylaxis diagnosis or therapy excluding failure to a produce the intended purpose (Karch & Lasagna 1975). As can be seen, the list in Table I does not completely adhere to that definition It is debateable whether an exaggeration of the therapeutic effect should be listed as a side effect, although it certainly can be regarded as an unwanted effect

ANTIHYPERTENSIVE THERAPY

Exaggeration of the therapeutic effect

Clearly antihypertensive therapy occasionally causes a pronounced reduction of arterial pressure thereby leading to complications as regards the central circulation, the peripheral circulation and maybe having its most drastic effects on the cerebral circulation. These aspects will be dealt with more in detail in the following three papers

Side effects

Toxic effects are experienced rarely with antihypertensive agents. As an example can be mentioned some forms of liver damage during treatment with alpha-methyl dopa.

Drug allergy is caused either by the drug itself or by a combination of the drug with protein (or a drug metabolite and protein) which forms an antigen that precipitates an allergic reaction. It is conceivable that the "practolol syndrome" and the hydralazine syndrome are caused by this mechanism.

Since many if not all, of the listed adverse effects in Table I will be dealt with more in detail during the symposium a final comment should only be made as regards the rebound effect. In reference to currently used antihypertensive agents clonidin is of particular

Table I Possible effects of pharmacotherapy

A. Therapeutic effect

B Adverse effects

a. Exaggeration of therapeutic effect

b Side effects

- toxic effects
- drug allergy
- idiosyncracy
- drug interaction
- carcinogenicity
- drug dependence
- mutagenicity
- theratogenecity
- placebo side effects

c Rebound effects

interest since this drug may cause a rapid and serious rise of blood pressure if treatment is stopped abruptly (Hansson et al 1973).

Finally in this brief analysis of unwanted effects of pharmacotherapy therapeutic failure has not been included. Obviously therapeutic failure can be due to either absolute or relative underdosage. However this should not in my opinion be considered as a side effect although some authors have chosen to include also therapeutic failure in listings of side effects.

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NEGATIVE CONSEQUENCES OF REDUCTION OF BLOOD PRESSURE – CENTRAL CIRCULATORY ASPECTS

Rune Sannerstedt

Antihypertensive drugs influence the circulatory system in various ways, apart from their therapeutic hypotensive action. The body's response to these, usually unwanted effects will vary depending on such factors as

1) the type of substance
2) the dose given
3) the length of treatment
4) the severity and nature of the hypertensive disease
5) the individual's posture and level of mental and physical activity
6) other concomitant medication

INFLUENCE ON REGULATION OF BLOOD PRESSURE

Postural hypotension due to sudden changes of posture or to the individual standing still for long periods is common, today particularly during treatment with postganglionic sympathetic inhibitors, e.g. bethanidine and guanethidine. It is mainly caused by reduced venous return, leading to pooling of blood in, above all, the lower extremities, and leads to objective symptoms in the form of dizziness and, in severe cases, *fainting attacks*. Postural hypotension may also occasionally occur during treatment with other drugs with an inhibitory effect on the sympathetic nervous system as well as during diuretic therapy, not least in geriatric patients with impaired homeostatic regulatory mechanisms owing to e.g. *age-related changes* in baroreceptor function.

Severe postural reactions and prolonged fainting have also been reported after use of the alpha-adrenoceptor blocker prazosin (not registered in Sweden), especially when too high doses are given initially, leading to the "first-dose" phenomenon.

Hypotension during physical exertion may occur during treatment with postganglionic sympathetic inhibitors, such as bethanidine and guanethidine, with a fall of blood pressure instead of the normal rise. This may manifest itself in the form of excessive tiredness and the fall of blood pressure may occasionally be so great that the patient faints, for example when cycling.

Paradoxical hypertension may occur during treatment with certain antihypertensive drugs and in severe cases may lead to hypertensive crises with hypertensive encephalopathy of varying severity. An example is clonidine, which may cause an acute catecholamine efflux, leading to a hypertensive crisis, if withdrawn abruptly. Parenteral administration of sympathetic inhibitors, such as bethanidine, guanethidine and *methyldopa, usually causes a transient* moderate rise of blood pressure initially. In patients with pheochromocytoma, however, they may provoke a considerable blood pressure rise by increasing the sensitivity of the blood vessels to circulating catecholamines.

INFLUENCE ON THE CONDUCTION SYSTEM

All antihypertensive drugs with an inhibitory effect on the sympathetic nervous system have, in principal, *a negative chronotropic action*, leading to bradycardia. As a rule, this effect is of no clinical importance except during treatment with β-adrenoceptor blockers, which sometimes cause excessive *sinus* bradycardia. Heart rate as low as 5–10 beats per minute has been reported. For the other sympathetic inhibitors, such as bethanidine, guanethidine, clonidine, methyldopa and reserpine, this risk is generally negligible at therapeutic dose level.

Peripheral vasodilators, such as hydralazines and minoxidil (which is not registered in Sweden), have *a positive chronotropic action* and frequently cause tachycardia. This tendency may be regarded as a compensatory reflex mechanism aimed at increasing the heart rate, and thus the cardiac output, in order to

counteract the blood pressure fall resulting from peripheral vasodilatation. A characteristic feature of the ß-adrenoceptor blockers is their *negative dromotropic effect*. In predisposed individuals the reduced conduction velocity may lead to atrioventricular block of varying degree.

Owing to their tendency to induce hypokalaemia, the diuretics could have *a positive bathmotropic effect*, i.e. they increase the excitability of the myocardium, with a consequent risk of ectopic beats and tachyarrhythmias.

INFLUENCE ON THE MYOCARDIUM

Another characteristic feature of the ß-adrenoceptor blockers, seen as a group, is their *negative inotropic effect*, leading to reduction of the contractile force of the myocardium. In predisposed patients this effect may lead to cardiac decompensation, which in early phases may present as a gradually increasing, radiologically demonstrable, cardiac volume. Treatment with ganglion blockers or postganglionic sympathetic inhibitors, such as bethanidine and guanethidine, may lead to *a reduced oxygen supply* to the myocardium and *coronary ischaemia*. The reduced oxygen supply is a result of reduced cardiac output and consequent reduced coronary blood flow. Clinically, this may result in angina pectoris. Cases of sudden death during the night, due to myocardial infarction, have also been attributed to drug induced hypotension. The previously mentioned positive chronotropic effect of the peripheral vasodilators, e.g. hydralazines, often leads to an overall *increase in cardiac work*. This may lead to a relative myocardial ischaemia, which in predisposed patients may manifest itself as angina pectoris.

INFLUENCE ON BLOOD VOLUME

Theoretically, all drugs with an inhibitory action on the sympathetic nervous system are liable to cause *hypervolaemia*, i.e. an increase in the volume of circulating blood. This effect is particularly marked during treatment with postganglionic sympathetic inhibitors such as guanethidine, but also occurs with, for example, methyldopa and clonidine. Fluid retention may also occur during treatment with some of the peripheral vasodilators. Thus, guancydine and minoxidil, neither of which is registered in Sweden, tend to cause massive fluid retention. Clinically, the hypervolaemia leads to development of resistance to the drug and the patient may observe a slight to moderate weight gain. In more severe cases declive oedema may occur and predisposed patients may develop cardiac decompensation.

Excessive diuretic therapy may lead to *hypovolaemia*, leading to a marked fall of blood pressure and postural reactions. In elderly patients, particularly, continued treatment may result in shock-like states.

INFLUENCE ON THE PULMONARY CIRCULATION

Increased pulmonary blood volume with pulmonary stasis, possibly progressing to manifest left heart failure and pulmonary oedema, may be expected in connection with hypervolaemia induced by sympathetic inhibitors.

Pulmonary congestion and related secondary pulmonary effects may explain the bizarre symptoms formerly seen during treatment with ganglion blockers. The syndrome was particularly common during treatment with hexamethonium and was therefore known as "hexamethonium lung".

Increased blood pressure in the pulmonary artery has been reported during treatment with peripheral vasodilators, e.g. minoxidil. The underlying mechanism for this pressure rise remains unclear.

FINAL COMMENT

Detailed descriptions of the negative effects on the circulatory system of antihypertensive drugs have been given in recently published monographs (Buurke 1977, Gross 1977, Tester Dalderup 1977). The multiplicity of these adverse effects, together with the facts that they often have a decisive influence on the therapeutic response, may represent a major problem during practical management of hypertensive patients.

A good knowledge of these points on the part of the doctor markedly improves the chances of achieving optimal blood pressure control with a minimum of subjective and objective unwanted effects and side effects from the circulatory system.

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EFFECT OF BLOOD PRESSURE REDUCTION ON TISSUE PERFUSION

Ramon Svensson

INTRODUCTION

The blood-flow in a tissue is determined by the perfusion pressure (arterial blood pressure minus venous blood pressure) and blood-flow resistance in the tissue according to the equation:

$$\text{Blood-flow} \approx \frac{\text{perfusion pressure}}{\text{resistance}}$$

From this equation follows that blood-flow will decrease when the perfusion pressure falls if resistance is unchanged. This is illustrated in Figure 1 which shows the effect of acute blood pressure reduction on hand blood-flow under maximal vasodilatation of the hand blood vessels.

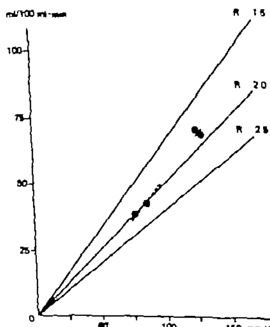


Figure 1 Hand blood-flow under maximal vasodilatation and mean blood pressure in a hypertensive patient, in whom an acute blood pressure reduction was induced by trimetaphan infusion. Isoresistance lines are given and R represents blood-flow resistance in relative units.

AUTOREGULATION OF BLOOD-FLOW

Under normal conditions, vascular resistance does not remain unchanged when blood pressure is reduced. Most tissues show some degree of *autoregulation* and in these tissues the resistance vessels compensate more or less completely for the blood pressure reduction by dilatation. This regulation has been ascribed to: a) an accumulation of vasodilating metabolites when blood flow tends to go down, b) a direct effect of the blood pressure on the vascular smooth muscle activity. By distending the small vessels and thus stretching the smooth muscle cells in the wall the blood pressure stimulates these cells to contraction. When the blood pressure falls and the tension in the smooth muscle cells is decreased, the activity in these cells is reduced, which causes the blood vessels to dilate compensatorily (Folkow 1964).

The degree of blood-flow autoregulation differs from one tissue to another. The autoregulation is most pronounced in tissues where the blood vessels are regulated mainly by local factors and in which the vasomotor nerves are of minor importance for the regulation of flow. It is best developed in vital organs, such as the brain, the kidneys (Figure 2), the intestines and the heart (Folkow & Neil 1971). Concerning the heart and the coronary circulation the situation is, however, somewhat more complex since blood pressure reduction also reduces the oxygen consumption and the metabolic need of the heart muscle. The skeletal muscles show a moderate degree of autoregulation. The skin blood vessels are mainly governed by the vasomotor nerves and show very little autoregulation.

It can thus be summarized that in tissues with pronounced autoregulation the blood-flow remains unchanged or almost unchanged until the blood pressure reaches such a low value that the capacity of the regulatory mechanism is exhausted. Below this lower

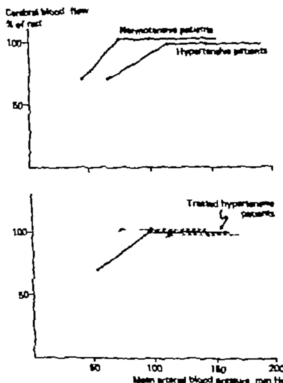


Figure 3 The upper panel shows mean curves of relating cerebral blood-flow to blood pressure in normotensive and severely hypertensive subjects The lower panel represents another group of patients with a formerly severe hypertension, which at the time of the study was effectively controlled by antihypertensive therapy From Strandgaard 1976 By permission

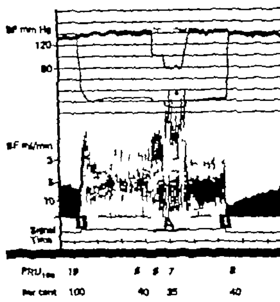


Figure 4 Effect of an experimental femoral artery occlusion on the hind limb blood-flow in the cat. Observe that blood-flow (BF) is recorded with drop recorder technique, which means that flow is inversely proportional to the height of the curve. Mean blood pressure (BP) is given proximal to ("systemic pressure") as well as distal to the occlusion ("local perfusion pressure") The figures at the bottom show vascular resistance in the hind limb (in relative units and per cent) Note the autoregulatory change in resistance when the artery occlusion is applied (↑) When the "local perfusion pressure" then is further reduced at A as a consequence of a "systemic pressure" reduction, blood-flow goes down and resistance remains unchanged, since the capacity for autoregulation is already used up From Thulesius 1962. By permission.

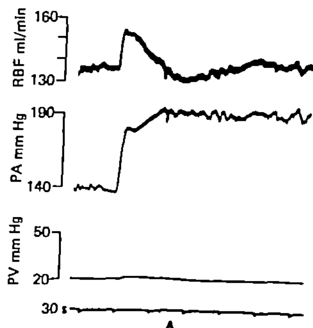
at a higher systemic blood pressure than normal (Figure 4)

Finally tissue blood-flow may be influenced by *changes in vascular tone* in the resistance vessels *induced by antihypertensive therapy* either by baroreceptor activation or by direct effects of the drug on the smooth muscle cells For example, ß-blockers are known to increase smooth muscle tone in the resistance vessels (Figure 5) Such an increase in *vascular tone reduces* resting blood-flow at normal perfusion pressure, but blood-flow under ischaemia or hypotension may also be affected at least in tissues where vasomotor nerves dominate the regulation of the blood-flow and where local factors are less important

CLINICAL ASPECTS ON BLOOD PRESSURE REDUCTION

The effects of blood pressure reduction on cerebral blood-flow are well known and will be dealt with elsewhere in these proceedings (Hansson 1978).

Concerning myocardial blood-flow a reduction of the systemic blood pressure implies not only a reduced perfusion pressure for the coronary vascular bed, but also a reduced work load and reduced oxygen need for the heart muscle. When ß-blockers are used for *the blood* pressure treatment, the oxygen need is further reduced due to the reduction in heart rate. For this *reason the need for a fully maintained coronary flow* does not exist and an aggravation of angina pectoris symptoms due to blood pressure lowering therapy is therefore uncommon with modern drugs.



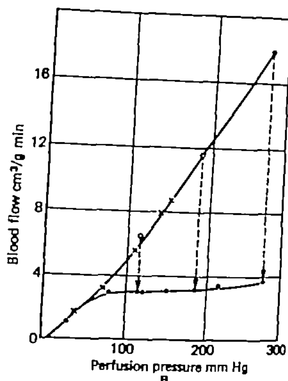


Figure 2. Acute (O–O) and long-term (●–●) effect of blood pressure change on renal blood-flow. From Semple & De Wardener 1959 (A), and Thurau & Kramer 1959 (B). By permission

limit for the autoregulation the blood-flow falls in parallel with the blood pressure. In tissues with less pronounced autoregulation the blood flow falls more or less in pace with the pressure drop over the whole pressure range.

BARORECEPTORACTIVATION AND BLOOD-FLOW

A blood pressure drop induces via the baroreceptors in the carotide sinus and the aortic arch an enhanced vasomotor nerve outflow to various vascular beds: resistance vessels (arteries and arterioles) as well as capacitance vessels (veins). Resistance vessels with a dominating local regulation are less affected than vessels which are strongly regulated by the nerves. During long term blood pressure change the baroreceptors "reset" to the new pressure level (Sleight 1975[a], Sleight 1975[b]). This means that after some time they "accept" the new blood pressure and tend to maintain it. This means in turn that the nerve activity is normalized.

EFFECT ON TISSUE BLOOD-FLOW OF BLOOD PRESSURE LOWERING TREATMENT

In patients with hypertension and cardiovascular disease the relationship between blood flow and blood pressure can be changed by several means.

Due to *structural changes* (Increased wall-lumen ratio) *in the resistance vessels* of patients with hypertension the shape of the pressure flow curve is changed so that the lower limit for the autoregulation (as well as the upper limit) is moved to the right (Figure 3). From this follows that the blood flow starts to fall at a higher blood pressure in patients with hypertension than in normotensive individuals. Hypertensive patients faint at a higher blood pressure level than normotensive persons do (Stead & Kunkel 1940).

Arteriosclerotic changes in the big arteries may also influence the flow pressure relationship in these patients. An arteriosclerotic occlusion or obstruction will reduce the local perfusion pressure in the tissue distal to the obstruction in relation to the systemic blood pressure. Therefore the local tissue blood-flow will fall

ARTERIAL HYPOTENSION AND ITS CONSEQUENCES FOR THE CEREBRAL CIRCULATION

Lennart Hansson

INTRODUCTION

The blood-flow of the human brain and its relation to arterial pressure has been studied extensively since Kety developed the inert gas method for determination of cerebral blood-flow (CBF) in 1945 (Kety & Schmidt 1945). The metabolic demands of the brain are comparatively high, resulting in a resting blood-flow of 50–60 ml per minute and 100 g of tissue under resting conditions. This means that approximately 750 ml per minute of arterial blood is needed for the maintenance of cerebral metabolism. This in turn, corresponds to almost 15 % of the resting cardiac output, and due to the high oxygen extraction of the brain means that approximately 20 % of the body's total oxygen consumption goes to this organ (Folkow & Neil 1971).

AUTOREGULATION OF CEREBRAL BLOOD-FLOW

As in so many other "peripheral" vascular beds, the blood-flow in the cerebral circulation is autoregulated. In other words the CBF is kept constant over a wide range of blood pressure and in this respect the brain is similar to e.g. skeletal muscle, kidney, liver and other organs or organ systems (Johnson 1964, Sivertsson 1978).

Findings suggesting autoregulation of blood-flow was first made by Bayliss (1902) who among other things studied the relationship between arterial blood pressure changes and volume changes in the hind limbs of various animals.

Bayliss also found autoregulation of blood-flow in other organs, such as the kidney, and concluded that it was independent of nervous influence (Bayliss 1902).

Several theories have been put forward in order to explain the autoregulation of blood-flow. One of these is the *myogenic theory*, which has been discussed e.g. by Folkow (1964).

In brief this theory depends on the concept that a basal tone exists in the blood vessels. A lowering of blood pressure would then represent a diminished stimulus and therefore lead to vasodilatation which in turn would tend to keep the flow unchanged.

Another theory put forward to explain flow autoregulation is the *metabolic theory* (Berne 1964). In brief this theory is based on the concept that changes in perfusion pressure will cause metabolic changes in the tissues, e.g. accumulation of metabolites which in turn may induce changes of the vascular calibers so that flow is kept constant.

The third main theory frequently referred to in discussions regarding autoregulation of CBF is the *tissue pressure theory*. This theory requires that the organ in question is surrounded by very rigid capsule such as the brain within the skull. Elevation of the perfusion pressure will then cause an outward filtration of fluid, which in turn will cause a raised tissue pressure which compresses the vessels to a certain extent thereby keeping flow constant.

The tissue pressure theory would seem to offer a logical explanation of the autoregulation of CBF when arterial pressure is raised. However, it is much more difficult to apply this theory in order to explain autoregulation of CBF also when blood pressure is lowered, and for this reason the tissue pressure theory would appear to offer a less likely explanation.

It is entirely possible that more than one mechanism of the above mentioned are involved in the autoregulation of CBF. Thus, Lassen has expressed the opinion that both the *myogenic theory* and the *metabolic theory* are engaged (Lassen 1959, Lassen 1964). This view has also been expressed by others working in this field, e.g. Harper and Häggendal (1968). Findings supporting the myogenic theory have been reported e.g. by Häggendal and Johansson (1966) and by Ekström-Jodal and co-workers (1969). Further support for the myog

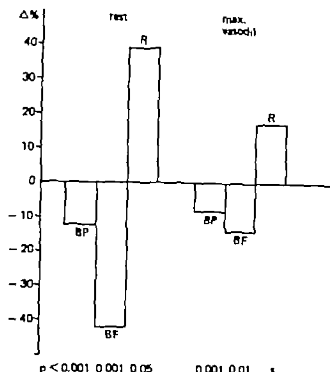


Figure 5 Change in the mean auscultatory blood pressure, calf blood-flow and calf flow resistance at rest and under maximal vasodilatation in a group of patients with mild to moderate blood pressure elevation during 6 weeks of propranolol therapy (320 mg per day range 80–640 mg per day) (n = 16). Vasodilatation was induced by a combination of artery occlusion and calf muscle work until exhaustion.

Reduction of perfusion pressure as regards the blood flow in the extremities is of particular interest in patients with impaired peripheral circulation, e.g. due to arterial disease as in intermittent claudication In such a patient reduction of systemic arterial pressure for example caused by antihypertensive therapy may cause an aggravation of ischaemic symptoms such as a further reduction in walking distance. In patients with incipient or manifest gangrene antihy pertensive therapy should be avoided if possible with respect to other manifestations of the high blood pressure in the patient Blood pressure lowering therapy will most likely aggravate the ischaemic symptoms in such patients. In fact treatment with drugs which increase blood pressure, has sometimes been used wi good therapeutic results in such patients (Lassen al 1968).

CONCLUSIONS

Blood flow in several important peripheral vascul beds is kept constant over a wide range of perfusio pressure (autoregulated) By means of blood pressur reduction below the lower limit of autoregulation e.g by antihypertensive therapy and particularly in tissue distal to local obstructions causing further reduction in the perfusion pressure, ischaemic symptoms o varying severity may follow These symptoms ma be severe enough to warrant a withdrawal of bloo pressure lowering treatment

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enic mechanism is offered by the finding that autoregulation takes place at a lower flow level with a pulsatile flow as compared to non pulsatile flow with the same mean pressure (Held et al 1969) It is interesting to note that the existence of autoregulation of the CBF has been denied by some distinguished researchers even into the 1960's (Sagawa & Guyton 1961) For further extensive discussions on the autoregulation of CBF the reader is referred to references: Lassen 1959 Lassen 1964 Harper 1966 & Ekström Jodal 1970

EFFECTS OF BLOOD PRESSURE CHANGE ON THE CEREBRAL BLOOD-FLOW

As already mentioned CBF is kept constant over a wide range of blood pressure. In fact Lassen suggests that CBF is unchanged at arterial pressures between 60–170 mm Hg (1959). This is supported by studies showing that neither essential hypertension (Moyer et al 1953 Moyer & Morris 1954 Hafkenschiel et al 1954), nor drug-induced hypertension (Moyer et al 1954) was associated with any significant change of CBF Moreover moderate reduction of blood pressure did not cause a significant change of CBF (Moyer & Morris 1954 McCall 1953).

That autoregulation of CBF cannot be maintained at low arterial pressure has been known for several decades (Lassen 1959) Later studies have demonstrated a breakthrough of autoregulation also at high blood pressures (Strandgaard et al 1973) Of great interest is the fact that the whole autoregulation curve of CBF is shifted to the right in hypertension (Figure 1) This has been demonstrated in hypertensive patients using angiotensin II and the ganglion blocker trimetaphan in order to raise and lower blood pressure respectively (Strandgaard et al 1973). Studies in normotensive baboons and in baboons with two-kidney-Goldblatt hypertension have confirmed this shift of the curve both as regards the upper (Strandgaard et al 1975) and the lower limit of CBF autoregulation (Jones et al 1976). It has been suggested (Strandgaard 1978) that the shift of the autoregulation curve in hypertension to the right is due to structural vascular changes in the precapillary resistance vessels leading to an increased wall to lumen ratio (Folkow et al 1973) (Figure 1).

CLINICAL IMPLICATIONS

When the lower limit of CBF autoregulation is reached a number of symptoms occur (Table I). Likewise, as blood pressure is increased to above the upper limit of CBF autoregulation Increasingly severe symptoms will be seen (Table II) Due to the shifted autoregulation curve hypertensive individuals will tolerate higher blood pressure levels before they experience the symptoms and consequences described in Table II On the other hand they will also be more susceptible to blood pressure reductions. Particularly when reducing very high blood pressures rapidly symptoms of reduced cerebral perfusion have been reported. Thus, Graham reported two patients with malignant hypertension who both became unconscious after having had their blood pressure reduced from 240/140 mm Hg to 120/85 mm Hg and from 240/170 mm Hg to 120/100 mm Hg respectively by administration of oral bethanidine and intravenous pentholinium respectively (Graham 1975). Particularly in elderly hypertensive patients care should be taken not to lower arterial pressure too rapidly (Jones & Graham 1977).

Certain drugs seem to require more care than other Thus sodium nitroprusside has been shown to increase intracranial pressure (Turner et al 1977). This is probably due to the powerful vasodilating action of this compound which could cause edema of the brain in spite of the reduction in perfusion pressure. In a series of 44 patients undergoing neurosurgery sodium nitroprusside was shown to give an initial increase in intracranial pressure whereas treatment with the

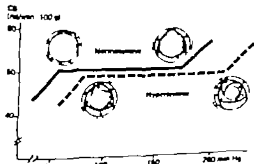


Figure 1 Cerebral blood-flow autoregulation curves in normotension and hypertension Note shift of curve to the right in hypertension due to structural changes in the precapillary resistance vessels (Based on Lassen 1959 Ekström-Jodal 1970, Moyer & Morris 1954 Strandgaard et al 1973 and Jones et al 1976)

ganglion blocker trimetaphan did not have this effect (Turner et al 1977). Furthermore, treatment with sodium nitroprusside may give rise to rapid changes in arterial pressure which are too fast for the autoregulation process to be maintained (Fitch 1977). It has also been claimed that CBF autoregulation is lost altogether during treatment with this compound (Crockard et al 1976).

From a practical point of view it therefore appears that special care should be taken when using sodium nitroprusside in situations requiring acute reduction of arterial pressure. During chronic treatment of hypertension particular care is recommended when using peripheral sympatholytic agents, which occasionally may reduce blood pressure drastically, e.g. in the standing position or during exposure to heat, with ensuing risks of reduced CBF leading to dizziness or syncope. On the other hand prolonged and gradual reduction of elevated arterial pressure in hypertension will tend to shift the autoregulation curve of CBF back towards normal (Strandgaard to be published). This is probably due to reversibility to the structural vascular changes in the precapillary resistance vessels of the kind described in other vascular beds (Hansson & Sivertsson 1975).

Table I. Effects of reduced cerebral blood-flow

Discomfort
Dizziness
Sleepiness
Nausea
Syncope
Coma
Death

Table II. Effects of increased cerebral blood-flow

Discomfort
Headaches
Nausea
Mental confusion
Convulsions
Coma
Death (apoplexy)

CONCLUSIONS

Cerebral blood-flow is autoregulated over a wide range of arterial pressure. This autoregulation of CBF is shifted towards a higher blood pressure range in hypertensive patients due to structural vascular changes in the precapillary resistance vessels. When reducing blood pressure below the lower limit of autoregulation, potentially dangerous effects may arise such as syncope or unconsciousness. These risks should be born in mind particularly when employing powerful and fast acting antihypertensive agents. On the other hand, prolonged and gradual reduction of arterial pressure through the use of oral antihypertensive agents will tend to shift the autoregulation curve of CBF back towards normal thereby minimizing the risk of cerebral complications due to reduced CBF.

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Ove Andersson

Coronary blood-flow is, of course, subject to autoregulation much as skeletal muscle flow. Although patients may occasionally experience intermittent claudication following reduction of arterial pressure attacks of angina pectoris seem to be rare. Would anybody like to comment on this

Rune Sannerstedt

I believe that this mainly reflects a change in therapeutic policy. Hydralazine in high doses and in conjunction with insufficient B-blockade may cause angina but this is an exception.

Lennart Hansson

Lowering of arterial pressure will favourably influence one of the most important factors in provoking angina, cardiac work. Cardiac oxygen consumption is to a large extent determined by heart rate multiplied by arterial pressure. Agents which decrease heart rate as well as blood pressure will thus tend to diminish the risk of provoking angina.

Sven Hedlund

In elderly patient further complicating factors may contribute to cause angina pectoris, e.g. AV-block, frequent extrasystolic beats, attacks of tachycardia or postural hypotension, all of which may diminish cerebral blood-flow

Lennart Hansson

In a majority of hypertensive patients, though, there is a breakthrough of cerebral blood-flow autoregulation when a sufficiently high blood pressure level is reached.

Olof Forssman

Does vasopressin have any role in the distribution of blood-flow to different tissues, e.g. the brain

Ramon Svertsson

I am not aware of studies relating to vasopressin and autoregulation but vasopressin is of interest mainly with regard to blood volume regulation.

Mats Danielson

Changes in blood viscosity may influence both central and peripheral circulation. Diuretics increase blood viscosity mainly in the initial period of treatment. Do you think that this effect may have clinical consequences

Lennart Hansson

Blood viscosity is almost invariably determined in vitro but this differs considerably from viscosity in vivo (Djojosugito et al. 1970). Dogs subjected to step-wise increases in blood loss do not show any significant changes in blood viscosity until the hematocrit value is considerably lowered. However a significant increase of cerebral blood-flow has been demonstrated in patients following reduction of hematocrit by venesection (Thomas et al. 1977). It is not likely though that the small decrease in plasma volume observed during treatment with diuretics will have functionally significant effects on blood viscosity

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ANTIHYPERTENSIVE DRUG REACTIONS FROM DIFFERENT ORGAN SYSTEMS AND FUNCTIONS – AN INTRODUCTION

Mats Henning

Adverse drug reactions may appear dose dependent being extensions of the pharmacological actions of the drug. They may also occur with little or no relation to the dosage mostly constituting allergic reactions. A clinically important aspect is that dose dependent drug reactions are to a large extent predictable and, hence, in many instances preventable. Such reactions make up for 70 to 80 per cent of unwanted drug responses. These facts emphasize the importance of an increased knowledge about side effects of drugs. The well-known truism that no clinically useful drug is devoid of toxicity should be a constant reminder to the clinician and urge to constant attention for the appearance of probable adverse reactions. Quantification and information are useful means for improving drug safety. It is the purpose of this part of the symposium to discuss in detail the individual tissue or organ untoward responses of antihypertensive drugs which will have to be considered in the all-important risk benefit relationship of therapy. It has been said that in the ratio adverse effects versus benefit we are uncertain not only of the nominator but also of the denominator. We hope that the presentations of this session will serve to increase the precision of the risk benefit quotient.

ADVERSE REACTIONS TO ANTIHYPERTENSIVE DRUGS REPORTED TO THE SWEDISH ADVERSE DRUG REACTION COMMITTEE

Gunnar Boman

A Swedish centre for monitoring of reports on adverse drug reactions (ADRs) was started in 1965 run by a temporary ad hoc committee. In 1971 the activity became permanent and was incorporated into the Department of Drugs, a part of the National Board of Health and Welfare. Since 1975 it is mandatory for all Swedish physicians and dentists to report a) all drug related fatal reactions, b) other serious ADRs and c) new and unexpected ADRs, from both new and old drugs. After the introduction of compulsory reporting about 2,000 reports have been received annually.

All reports are primarily assessed by a medical officer sometimes after requests for supplementary information. The Adverse Drug Reaction Committee then classifies the causal relationship between the suggested ADR and one or more involved drugs. Relevant details of each report, even those classified as "unlikely" are stored in a computer register and also forwarded to the WHO Collaborating Centre for International Drug Monitoring. In the following all figures relate to reports with a causal relationship classified as "probable" or "not excluded". It should be noted that the figures for 1977 are preliminary.

ADVERSE REACTIONS TO ANTIHYPERTENSIVE DRUGS IN GENERAL

For this presentation antihypertensive drugs are defined as drugs included in the following pharmacological groups of the Swedish Register for Pharmaceutical Specialities: Group 2B 12 (beta-receptor blocking agents, "beta-blockers"), 2E (antihypertensive agents) and 2F (diuretics). This means that e.g. beta-blockers used for angina pectoris and diuretics for cardiac insufficiency also will be included. Information on the specific indication is seldom available in the individual reports.

During the last 8 years of operation 10-20 per cent of all reports to the Adverse Drug Reaction Committee have been related to antihypertensive drugs as defined above (Figure 1). ADRs related to cardiovascular drugs in general constitute the second largest group of reports during the last years. Reports on antibiotic drugs are the most frequent.

SALES OF CARDIOVASCULAR DRUGS

As a background for the following discussion the sales figures for 1977 regarding beta-blockers and antihypertensive agents are presented in Table I. The sales statistics for diuretics are not included. The sales figures have been calculated as Defined Daily Doses (DDD) and kindly provided by Ingrid Nordenstam, Apoteksbolaget (National Corporation of Pharmacies), Stockholm. The concept of DDD enables a better comparison between the consumption of different drugs than the cost or the number of packages. A preliminary list of DDD for drugs used in Sweden is available from Apoteksbolaget.



Figure 1. Reports on adverse reactions to antihypertensive drugs in per cent of all reports received by the Swedish Adverse Drug Reaction Committee.

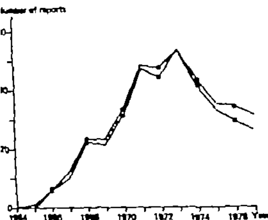


Figure 3. Annual number of reports on adverse reactions to sympatholytic agents (●), thereof to methyldopa (■)

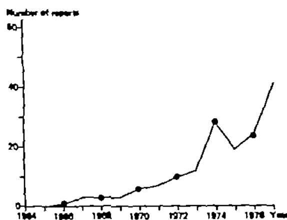


Figure 4. Annual number of reports on adverse reactions to hydralazine

ADVERSE REACTIONS TO SYMPATHOLYTIC AGENTS

Reports on reactions to sympatholytic agents increased in number up to 1973 (53 reports) but have then declined by each year (Figure 3). This decline probably reflects the diminishing use of this group of drugs. More than 90 per cent of the 389 reactions reported for this group concern adverse effects of methyldopa. The reports on methyldopa during 1965–1975 have recently been analysed (Furhoff 1978).

ADVERSE REACTIONS TO HYDRALAZINE

Reactions to hydralazine have been reported in increasing numbers during recent years (Figure 4), probably reflecting the increasing use of this drug. In total 157 reports have been received. A peak of 28 reports was observed in 1974 in connection with a study of acetylator status in patients with hydralazine induced lupoid syndrome reported to the Committee (Strandberg et al. 1976).

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Swedish ADR Committee. Report no 22. Läkartidningen 72: 2697–2699, 1975.

Table I. Sales of cardiovascular drugs in Sweden 1977 Source: National Corporation of Pharmacies, Stockholm. 2B 12 = Beta-receptor blocking drugs. 2E = Antihypertensive drugs. DDD = Defined Daily Doses/1.000 inhabitants/day

	DDD	
	2B 12	2E
National average	34	13
County		
Stockholm	24	9
Gothenburg	43	14
Gotland	48	14
Värmland	47	16
Örebro	42	22

Table I shows that beta-blocking agents are used twice as much as other antihypertensive agents. Impressive regional differences are also observed 24–48 DDD/1 000 inhabitants/day for the beta blockers and 9–22 for antihypertensive agents" Some examples of regions with obvious deviations from the national average are also shown A futher analysis of the material must be performed before any explanations can be suggested

ADVERSE REACTIONS TO BETA BLOCKERS AND THIAZIDES

The annual numbers of received reports, related to beta-blockers and to thiazides and thiazide like diuretics are shown in Figure 2. In total 365 reports on beta-blockers and 316 reports on these diuretics have been submitted. In the latter group 69 reports on a combination of hydrochlorothiazide and amiloride (Moduretic) are not included. Few adverse reactions to the beta-blockers were reported until 1974 when reports on practolol caused an impressive increase. It is interesting to note that even after the withdrawal of practolol in 1975 the number of reports on beta blockers have remained high One explanation is the introduction of new beta-blockers during the last years Another is that the practolol incident made the doctors aware of the fact that this group of drugs *really* can cause adverse reactions. The reporting pattern for the diuretics is different After a peak of 36 reports in 1969 the numbers have been constant, i e. showing a decreasing share in view of the increase in the total reporting in Sweden

ADVERSE REACTIONS TO PRACTOLOL

Practolol (Eraldin) was introduced on the Swedish market in March 1974 During May and June 1974 preliminary reports on serious ocular and cutaneous reactions to practolol were published in the British Medical Journal Single reports on adverse reactions were received in the following month In November 1974 the Department of Drugs in view of continued reports in the literature informed all Swedish physicians of these risks and recommended a restriction of the use of practolol In the following 3 months 20–30 reports on reactions to practolol were received each month More than 100 reactions were reported before the withdrawal of practolol for oral use in May 1975 (Swedish ADR Committee 1975) It can be noted that no cases of pleurisy or sclerosing peritonitis related to practolol have been reported in Sweden

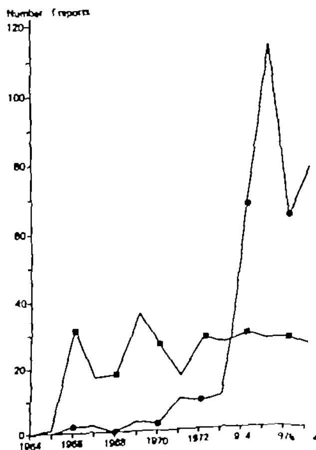


Figure 2 Annual number of reports on adverse reactions to beta-receptor blocking agents (●) and thiazide diuretics (■)

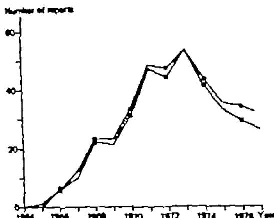


Figure 3 Annual number of reports on adverse reactions to sympatholytic agents (●), thereof to methyldopa (■)

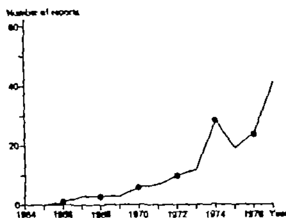


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REGISTRATION OF SIDE EFFECTS BY MEANS OF A QUESTIONNAIRE

Ove Andersson

INTERVIEWER BIAS

It is common knowledge among clinicians in all branches of medicine that details of the patient's symptom picture will often be missed if the patient is not specifically asked whether or not he has had various relevant symptoms. The same situation applies concerning side effects of for example, antihypertensive drugs. This phenomenon is registered objectively through the differences in the incidence of side effects when only *spontaneously* reported symptoms are recorded and when patients are interviewed according to a standardized *check-list*. Since there is reason to suspect some degree of under-reporting, owing, among other factors, to the patient's positive attitude towards the therapist, *self-administered questionnaires* have been introduced for registration of side effects in recent years. The advantages of this approach are obvious: the patient is given an opportunity to report any symptoms at his leisure, without being influenced by the doctor or nurse. The doctor's enthusiasm for a certain mode of therapy can be neglected, especially in comparative trials of double-blind type.

The method also has obvious disadvantages, however there is a loss of sensitivity as the questionnaire must be kept reasonably short, the patient may have difficulty understanding the questions and finer points may be missed unless supplementary questions are asked. The following questionnaire (Table I), which has been used for registration of side effects in comparative studies of ß-adrenoceptor blocking agents and diuretics, may serve as an example of a self-administered questionnaire.

INFLUENCE OF THE PATIENT MATERIAL ON THE INCIDENCE OF SIDE EFFECTS

The composition of the patient material with respect to sex, age and organic manifestations of hypertension obviously influences the incidence and nature of reported side effects. There is no other way to explain how the incidence of tiredness as a side effect of methyldopa can vary between 12 and 83 % in two different studies (Amery et al. 1970, Prichard et al. 1968). There are admittedly other differences between these studies, but this example would seem to provide a good illustration of the difficulties in interpreting results from trials in different groups of patients.

Bulpitt et al (1974) have reported clear sex differences in a large trial with overrepresentation of headache, depression of mood and changes of therapy in women compared to men. Although details of treatment effect on blood pressure, age and severity of hypertension are lacking, the material is so large (over 400 patients in each group) that only marked selection in connection with admission of the patients to the study can reduce the general applicability of the findings. Increasing age, which often means an increased frequency of organ damages as well as of co-existing diseases, also leads to an increased incidence of reported side effects such as reduced rate of walking, nycturia, reduced sexual potency and postural hypotension (Bulpitt et al. 1974). On the other hand, elderly patients suffered less from headache, depression of mood and somnolence in the same study

FREQUENCY OF SYMPTOMS – COMPARISON BETWEEN HYPERTENSIVES AND HEALTHY CONTROLS

When assessing the frequency of symptoms in arterial hypertension reported in self-administered questionnaires it would seem logical to compare healthy subjects with groups of hypertensive patients. A randomized material of healthy and hypertensive 50-year-old men, homogeneous with respect to sex and age has been studied in Gothenburg (Berglund 1974). A questionnaire comprising 30 questions about the occurrence of symptoms during the preceeding three

Table 1 An example of a self-administered questionnaire.

Code: No = 1 Uncertain = 2 Yes = 3

General question to be asked first

Do you think that you have had any side effects of the medicine? If "yes" please state what kind of side effects ☐

I am going to ask you some questions about symptoms that you may have had and I want you to try to remember whether you have had these symptoms or not. (If the patient replies "yes" ask him "Has this been troublesome?")

Have you been troubled by breathlessness and wheezing in your chest?	☐
Have your ankles become swollen in the evening?	☐
Do you think that your condition in the whole has deteriorated?	☐
Have you had any pain in your chest when going uphill or climbing stairs or at other times when you have exerted yourself?	☐
Have you had any pain in your calf muscles when walking uphill or climbing stairs or when hurrying on even ground?	☐
Do you often have cold hands or feet?	☐
Have you noticed whether your heart beats especially slowly?	☐
Have you noticed whether your heart beats irregularly	☐
Have you become dizzy or has everything gone black when you get up	☐
Have you felt dizzy when walking about?	☐
Have you felt nauseated after taking the tablets?	☐
Have you had stomach ache?	☐
Have you had diarrhoea?	☐
Have you been more than usually tired?	☐
Have you felt depressed?	☐
Have you had any difficulties in getting to sleep at night	☐
Have you often woken up during the night?	☐
Have you had nightmares	☐

months was used (Lindström & Tibblin 1971). These questions were intended to measure the subject's tendency to report symptoms and concerned both somatic and more unspecific and mental symptoms. The results can be summarized as follows: There were no significant differences in the incidence of symptoms between a reference group, an untreated group and a group of patients receiving antihypertensive therapy. A non significant tendency towards a higher incidence of many symptoms was recorded in the group of treated hypertensives.

Findings obtained in a study in London (Bulpitt et al. 1974) contrast with these results. In age- and sex-matched materials a significantly higher rate of reporting of symptoms was found among hypertensives with respect to postural hypotension, dryness of the mouth, nycturia, diarrhoea, somnolence, low walking speed, impotence and disturbance of ejaculation. The mean age of the patients and their controls was 55 and 53 years, respectively.

The essential difference between these two studies is that the Gothenburg study concerned general symptoms, whereas the London study comprised specific questions about side effects that commonly occur during the treatment given. The high rate of these subjective side effects is also characteristic in association to treatment with drugs like methyldopa, bethanidine, guanethidine and reserpine.

INCIDENCE OF SYMPTOMS – COMPARISON BETWEEN BEFORE AND AFTER ANTIHYPERTENSIVE TREATMENT

Whereas comparisons between different groups of patients are difficult, for reasons discussed above, the self-administered questionnaire seems better suited for repeated registration in the same material. The questionnaire must then be adjusted to the therapy prescribed and symptoms should be recorded before and during treatment. The patients may then be divided into four groups:

a) patients without symptoms,
b) patients with the same symptoms before and during treatment
c) patients with new symptoms (side effects?) and
d) patients whose symptoms disappear

The British are pioneers in this field too. In a follow up study before and after ten months in 55 normotensive healthy subjects, a spontaneous improvement in most of the previously listed symptoms was recorded (Bulpitt et al. 1976). The difference between abolished and acquired symptoms tended to be positive. Repeated registration of symptoms before and after treatment of 110 hypertensives showed exactly the same trend.

In our own studies we have used a somewhat different approach when evaluating symptoms reported in questionnaires. As a rule, only new symptoms occurring during the treatment have been registered as an expression of side effects. In a comparative study of the hypotensive effect and biochemical and subjective side effects during treatment with hydrochlorothiazide at different dose levels, we found a significant reduction in the incidence of reported symptoms with reduction of the dose (Berglund & Andersson 1976). Since the three dose regimes were given in randomized order the reduction in symptoms cannot have been due to the time factor. In another comparative study (Andersson et al. 1976), in which 106 previously untreated patients with mild hypertension were randomly allocated to treatment with bendroflumethiazide (Salures K, 1–2 tablets) or propranolol (Inderal 160 mg once or twice a day), we found no decisive difference during the first twelve months of the study with respect to the effect on the blood pressure or biochemical changes. The incidence of reported symptoms fell significantly during the first two months of treatment with both drugs. A further reduction was observed in both groups during the treatment, few positive reports being registered.

SUMMARY

1. Self-administered symptom or side-effect questionnaires may be used to avoid observer bias.
2. Differences in symptom reporting occur between men and women and between different age-groups.
3. The incidence of symptoms declines with time in healthy normotensive controls.
4. With suitable questions, relating to specific side effects, registration of side effects is possible.
5. A causal relationship between side effects and treatment can only be verified by discontinuing the therapy and seeing whether the symptom disappears.
6. Placebo effects can never be excluded.

CONCLUSIONS

A self-administered questionnaire may be used for follow-up of treatment but should always be supplemented with the therapist's own assessment and evaluation of the connection with the treatment and degree of severity.

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DISCUSSION

Bengt Lundh

Adverse drug reactions are certainly not reported to their true extent and I wonder whether the representatives for the Adverse Drug Reaction Committee have any comments on the difference between the reported and the true incidence of side effects of drugs?

Gunnar Boman

Strictly by definition, all hypokalemias digitalis intoxications, insulin induced comas etc. which are associated with hospital care should be reported. This is of course not done and we would like to emphasize the importance of reactions of a somewhat less commonplace character

Also cases of suspected side effects should be reported Studies of drug induced blood dyscrasias show that one third of all hospitalized patients were reported to the committee.

ADVERSE REACTIONS TO ANTIHYPERTENSIVE DRUG THERAPY CENTRAL NERVOUS SYSTEM

Matts Henning

The introduction of reserpine and other extracts of Rauwolfia into antihypertensive treatment and the ensuing outbreak of reserpine-induced depressions made physicians painfully aware of central nervous side effects of antihypertensive agents. It should be noted that unwanted effects of this kind are frequently very difficult to anticipate from animal experiments and depend almost entirely on a careful clinical assessment. So far surprisingly little quantitative information is available on this subject. It appears that a major reason why so little attention has been paid to this aspect in clinical trials is related to the inherent difficulties in separating central nervous symptoms, caused by pharmacological actions of the drugs concerned, from secondary reactions to other side effects, or to other factors, e.g. the effect of being diagnosed as a victim of a life-long disease with treatment according to this.

In attempting to classify central nervous side effects of antihypertensive agents several possibilities arise. The simple process of cataloguing the various drugs and their reported side effects has been avoided. It is clear that drugs interfering with central nervous system (CNS) neurotransmitter metabolism are liable to affect various systems utilizing such transmitters, and a classification might be accordingly based. However, in many instances the precise nature of the influence of antihypertensive drugs on central neurotransmitters is not known and therefore a more clinically oriented approach to classification of CNS side effects has been adopted using the type of symptoms as a basis (Table 1). No attempt has been made to cover the full panorama of CNS side effects as found in e.g. Physician's Desk Reference or package inserts. CNS reactions secondary to the lowering of blood pressure are considered elsewhere in this symposium. Whenever possible reference has primarily been made to papers of review character.

I MENTAL CHANGES

A Sedation

The term sedative effect is notoriously vague in its definition and is observed with most drugs including placebo. Sedation is also not easily defined in psychological terms and the physiological and pharmacological basis for a sedative action is obscure. Common clinical translations of sedation would appear to be drowsiness, weakness, feeling of lassitude, fatigue or sleepiness during the day. Symptoms such as decrease in ability to concentrate, forgetfulness and prolongation of reaction time are probably other representations of sedation.

As might be expected the patient's experience of this will vary considerably depending on mental set up, activities etc. People engaged in intellectually demanding tasks will naturally suffer more from a sedative effect as will of course those employed in work requiring constant alertness and attention, e.g. operating complicated machinery or driving a car.

Table 1 Central nervous side effects of antihypertensive drugs

1	Mental changes	
	A Sedation	clonidine methyldopa reserpine β-adrenergic receptor blockers
	B Depression	reserpine methyldopa β-adrenergic receptor blockers
2	Sleep disturbances	β-adrenergic receptor blockers clonidine reserpine
3	Extrapyramidal symptoms	reserpine methyldopa
4	Neuroendocrinological symptoms	reserpine methyldopa

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Also cases of suspected side effects should be reported Studies of drug-induced blood dyscrasias show that one third of all hospitalized patients were reported to the committee.

may produce depressional states by a direct action on the CNS. The common denominator seems to be that these agents interfere with the metabolism of CNS neurotransmitters involved in the regulation of mood etc., notably 5-hydroxytryptamine. The best known example of this is the Rauwolfia alkaloids such as reserpine. Several records of reserpine-induced suicidal depression are available (see Goodwin & Bunney 1971 Tester Dalderup 1975) but the picture includes a full spectrum of symptoms down to quite subtle changes of mood. The incidence of depression during reserpine treatment varies considerably in the literature, many investigators failing to observe significant differences in this respect compared to control groups while other studies indicate figures as high as 25 per cent (Tester Dalderup 1975). While some of the factors mentioned earlier may contribute to obscure the true incidence it is my personal belief that, using careful diagnostic criteria, the proportion of patients showing reserpine induced depressive symptoms is really quite high and well motivates the declining usage of this drug in many countries. Apparently the risk increases with large doses but it should be noted that long-term treatment with even small doses affect CNS 5-hydroxytryptamine stores similarly as do large doses for brief periods (Rand & Jurevics 1977).

Methyldopa also depletes CNS monoamine stores although by a mechanism of action different from that of reserpine and affecting chiefly catecholamines; in fact, the antihypertensive effect of methyldopa is largely related to this central effect (Henning 1975). It is not known whether the feeble action of methyldopa on central 5-hydroxytryptamine metabolism explains why this drug is considerably less likely to cause depression than the Rauwolfia alkaloids but it seems quite clear from the literature that frank depression during methyldopa treatment is rare (Tester-Dalderup 1975 Tester Dalderup 1978). In fact some investigators found no significant association between methyldopa and depression (Dollery & Bulpitt 1975 Snaith & McCoubrie 1974) or in one instance not between any of the antihypertensive drugs studied (reserpine, methyldopa and adrenergic blocking agents) and the occurrence of depressive symptoms (Bant 1974). This author concludes that depressions occurring during antihypertensive drug therapy are reflections of the hypertensive disease itself. In spite of this it seems safest to avoid methyldopa in patients with a history of psychiatric disturbance of the depressive type.

The B-adrenergic blocking agents so frequently used in antihypertensive treatment have recently been incriminated in depressional states (Greenblatt et al. 1976, Robinson 1978) but a clear-cut dissociation from peripheral effects of B-adrenergic receptor blockade is hardly possible. In view of the previously mentioned pharmacological prerequisites (Conway et al. 1978) a careful observation of the B-blocker treated patient for the appearance of symptoms of depression would seem indicated. Rare reports of confusional or stuporous states, particularly in elderly people have been associated with B-blocking drugs (Robinson 1978).

Clonidine and its congeners also influence central neurotransmitter metabolism and, like methyldopa, their hypotensive effect depends on an interaction with central catecholamines (Henning 1975). As mentioned sedation is the outstanding central side effect of clonidine and depressional states are but rarely reported, it would appear that most if not all such cases fall within the categories (b) and (c) listed above. The same probably holds true also for the occasional reports of depression associated with other antihypertensive drugs (Bant 1974, Tester Dalderup 1975 Tester-Dalderup 1978). In one study patients treated with adrenergic neurone blockers of the guanethidine type tended to be more depressed than those on reserpine and methyldopa (Bant 1974) but this is undoubtedly secondary to the severe peripheral side effects of the neurone blockers.

2 SLEEP DISTURBANCES

The physiological mechanisms underlying sleep-wakefulness regulation are little known but catecholamine pathways from part of the brainstem reticular formation and particularly noradrenaline neurons seem to play a role in such functions (Lidbrink 1974). Drugs interfering with the function of catecholamine neurons are known to affect sleep-wakefulness control: all the agents discussed in the previous section have documented effects on various aspects of this parameter (Greenblatt et al. 1976, Robinson 1978, Tester

The antihypertensive drugs most frequently reputed to affect such activities are nowadays no doubt methyldopa and clonidine reserpine being less commonly employed (Tester Dalderup 1975) The pharmacological basis for the sedative effect of these drugs is probably related to their interfering with central adrenergic neurone systems which are engaged in the regulation of wakefulness and alertness (Lidbrink 1974) The incidence of troublesome sedation in patients taking these drugs is dose-dependent but probably quite high amounting in one careful survey to 51% for methyldopa (Dollery & Bulpitt 1975) With clonidine it appears to be even more common Onesti et al (1971) in a series of 90 patients on oral clonidine report sedation in 64% Recent studies have indicated that the sedative action of methyldopa may be diminished without losing the antihypertensive effect by giving the drug as a single dose at bedtime (Wright et al 1976) So far no reports are available on the possible influence of this procedure on sleep quality A decrease in mental acuity forgetfulness and prolongation of reaction time are other symptoms reported after methyldopa (Tester Dalderup 1975). A number of experimental agents pharmacologically related to clonidine seem to share the sedative effect with this drug (see e.g. Jääskelä 1976).

Treatment with ß-receptor blocking drugs is almost invariably associated with a feeling of tiredness, drowsiness or lassitude. That these agents do exert a sedative action by a direct effect on the CNS is highly probable; the existence of central adrenergic receptors of the ß-type is by now fairly well established (see Conway et al 1978) and these drugs are currently being tried in various neuro-psychiatric disorders including anxiety and similar symptoms (Symposium 1976). However it is not known to what extent the peripheral effects of ß-blockade, e.g. lowering of cardiac output and blood pressure and alterations in tissue perfusion may contribute to cause what the patient experiences as a feeling of tiredness etc. Further the sedative effect of ß-blocking drugs is considerably less troubling than for the drugs previously discussed and is usually of little concern compared to other central side effects (vide infra)

Out of other antihypertensive drugs reported to elicit sedative effects, diuretics (Dollery & Bulpitt 1975) and agents blocking peripheral sympathetic nerve function (e.g. ganglion blocking agents, guanethidine or bethanidine) are occasionally mentioned In these cases, sedation might be secondary to other actions of these drugs, e.g electrolyte disturbances or orthostatic reactions.

Drug treatment associated with heavy sedation may secondarily lead to disturbances of male sexual functions. This seems to be the case with methyldopa and clonidine both of which although not interfering directly with erection or ejaculation (Dollery & Bulpitt 1975) have been reported to cause impotence (Tester Dalderup 1975).

B Depression

As in the case of sedation there are both semantic and diagnostic problems associated with the evaluation of mental depression as a side effect of drug therapy: patients as well as physicians may differ in their criteria when applying the term depression. However it will usually be expressed as a psychic disturbance of varying severity including one or several of the symptoms of spontaneously occuring endogenous depression, i.e. lowering of mood, anxiety and psychomotor inhibition. A few studies are available (Bant 1974 Snaith & McCoubrie 1974) in which special psychiatric rating scales have been employed to quantitate the data, however the majority of investigators use the term depression with little or no diagnostic specification

When attemping to relate antihypertensive drug therapy to depression it must be taken into account that this may be caused by (a) the antihypertensive agent(s) administered either primarily due to CNS actions or secondarily due to other side effects (e.g. orthostatic reactions impotence etc); (b) a secondary reaction to the psychological consequences of being diagnosed as the victim of hypertension (c) a pure coincidence with spontaneous depression occurring during the treatment. Incidentally this leads to the interesting question whether depressive illness is perhaps more commonly associated with hypertensive disease.

In the individual case it is probably often impossible to systematize in the way outlined above but it seems quite clear that a number of antihypertensive drugs

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The ß-adrenergic blocking agents so frequently used in antihypertensive treatment have recently been incriminated in depressional states (Greenblatt et al. 1976, Robinson 1978) but a clear-cut dissociation from peripheral effects of ß-adrenergic receptor blockade is hardly possible. In view of the previously mentioned pharmacological prerequisites (Conway et al. 1978) a careful observation of the ß-blocker treated patient for the appearance of symptoms of depression would seem indicated. Rare reports of confusional or stuporous states, particularly in elderly people have been associated with ß-blocking drugs (Robinson 1978).

Clonidine and its congeners also influence central neurotransmitter metabolism and (like methyldopa, their hypotensive effect depends on an interaction with central catecholamines (Henning 1975). As mentioned sedation is the outstanding central side effect of clonidine and depressional states are but rarely reported, it would appear that most if not all such cases fall within the categories (b) and (c) listed above. The same probably holds true also for the occasional reports of depression associated with other antihypertensive drugs (Bant 1974, Tester Dalderup 1975, Tester Dalderup 1978). In one study patients treated with adrenergic neurone blockers of the guanethidine type tended to be more depressed than those on reserpine and methyldopa (Bant 1974) but this is undoubtedly secondary to the severe peripheral side effects of the neurone blockers.

2. SLEEP DISTURBANCES

The physiological mechanisms underlying sleep-wakefulness regulation are little known but catecholamine pathways from part of the brainstem reticular formation and particularly noradrenaline neurons seem to play a role in such functions (Lidbrink 1974). Drugs interfering with the function of catecholamine neurons are known to affect sleep-wakefulness control, all the agents discussed in the previous section have documented effects on various aspects of this parameter (Greenblatt et al. 1976, Robinson 1978, Tester

The antihypertensive drugs most frequently reputed to affect such activities are nowadays no doubt methyldopa and clonidine reserpine being less commonly employed (Tester Dalderup 1975) The pharmacological basis for the sedative effect of these drugs is probably related to their interfering with central adrenergic neurone systems which are engaged in the regulation of wakefulness and alertness (Lidbrink 1974) The incidence of troublesome sedation in patients taking these drugs is dose-dependent but probably quite high amounting in one careful survey to 51% for methyldopa (Dollery & Bulpitt 1975) With clonidine it appears to be even more common, Onesti et al (1971) in a series of 90 patients on oral clonidine report sedation in 64% Recent studies have indicated that the sedative action of methyldopa may be diminished without losing the antihypertensive effect by giving the drug as a single dose at bedtime (Wright et al 1976) So far no reports are available on the possible influence of this procedure on sleep quality A decrease in mental acuity forgetfulness and prolongation of reaction time are other symptoms reported after methyldopa (Tester Dalderup 1975). A number of experimental agents pharmacologically related to clonidine seem to share the sedative effect with this drug (see e.g. Jäätelä 1976)

Treatment with ß-receptor blocking drugs is almost invariably associated with a feeling of tiredness drowsiness or lassitude That these agents do exert a sedative action by a direct effect on the CNS is highly probable; the existence of central adrenergic receptors of the ß-type is by now fairly well established (see Conway et al 1978) and these drugs are currently being tried in various neuro-psychiatric disorders including anxiety and similar symptoms (Symposium 1976). However it is not known to what extent the peripheral effects of ß-blockade, e.g. lowering of cardiac output and blood pressure and alterations in tissue perfusion may contribute to cause what the patient experiences as a feeling of tiredness etc Further the sedative effect of ß-blocking drugs is considerably less troubling than for the drugs previously discussed and is usually of little concern compared to other central side effects (vide infra).

Out of other antihypertensive drugs reported to elicit sedative effects diuretics (Dollery & Bulpitt 1975) and agents blocking peripheral sympathetic nerve function (e.g ganglion blocking agents guanethidine or betanidine) are occasionally mentioned. In these cases, sedation might be secondary to other actions of these drugs e.g. electrolyte disturbances or orthostatic reactions.

Drug treatment associated with heavy sedation may secondarily lead to disturbances of male sexual functions. This seems to be the case with methyldopa and clonidine both of which although not interfering directly with erection or ejaculation (Dollery & Bulpitt 1975) have been reported to cause impotence (Tester Dalderup 1975).

B Depression

As in the case of sedation there are both semantic and diagnostic problems associated with the evaluation of mental depression as a side effect of drug therapy patients as well as physicians may differ in their criteria when applying the term depression However it will usually be expressed as a psychic disturbance of varying severity including one or several of the symptoms of spontaneously occuring endogenous depression i.e. lowering of mood anxiety and psychomotor inhibition A few studies are available (Bant 1974 Smith & McCoubrie 1974) in which special psychiatric rating scales have been employed to quantitate the data, however the majority of investigators use the term depression with little or no diagnostic specification.

When attemping to relate antihypertensive drug therapy to depression it must be taken into account that this may be caused by (a) the antihypertensive agent(s) administered either primarily due to CNS actions or secondarily due to other side effects (e.g. orthostatic reactions, impotence etc); (b) a secondary reaction to the psychological consequences of being diagnosed as the victim of hypertension, (c) a pure coincidence with spontaneous depression occurring during the treatment Incidentally this leads to the interesting question whether depressive illness is perhaps more commonly associated with hypertensive disease

In the individual case it is probably often impossible to systematize in the way outlined above but it seems quite clear that a number of antihypertensive drugs

may produce depressional states by a direct action on the CNS. The common denominator seems to be that these agents interfere with the metabolism of CNS neurotransmitters involved in the regulation of mood etc., notably 5-hydroxytryptamine. The best known example of this is the Rauwolfia alkaloids such as reserpine. Several records of reserpine-induced suicidal depression are available (see Goodwin & Bunney 1971 Tester-Dalderup 1975) but the picture includes a full spectrum of symptoms down to quite subtle changes of mood. The incidence of depression during reserpine treatment varies considerably in the literature many investigators failing to observe significant differences in this respect compared to control groups while other studies indicate figures as high as 25 per cent (Tester Dalderup 1975). While some of the factors mentioned earlier may contribute to obscure the true incidence it is my personal belief that, using careful diagnostic criteria, the proportion of patients showing reserpine induced depressive symptoms is really quite high and well motivates the declining usage of this drug in many countries. Apparently the risk increases with large doses but it should be noted that long-term treatment with even small doses affect CNS 5-hydroxytryptamine stores similarly as do large doses for brief periods (Rand & Jurevics 1977).

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Dalderup 1975 Tester Dalderup 1978). The table lists ß-blockers, clonidine and reserpine but it is difficult to establish whether any clearcut difference exists between the three drugs. The ß-blocking agents through their common use will be recognized as most commonly causing disturbances of sleep ranging from insomnia to vivid sometimes hallucinatory dreams somnambulism and violent behaviour with ensuing amnesia. These sometimes alarming but rarely serious central side effects of ß-blocking agents can be prevented or minimized by administering the major part or the full daily dose of the drug early in the day avoiding dosage at night. It has been claimed that certain ß-blocking agents are less prone to this type of side effect and this has been related to a poor penetration through the blood brain barrier (Robinson 1978). Although these agents certainly differ in their avidity to pass this barrier it is doubtful whether such differences are of significance in the clinical situation involving long term treatment in which some kind of an equilibrium is probably established. Carefully controlled studies allowing a settlement of this issue are not available but certainly called for.

Clonidine has been reported to cause insomnia and vivid dreams (Tester Dalderup 1975) but the incidence of this side effect is probably lower than after ß-blockers. Reserpine treatment may lead to an increase in the duration of paradoxical (REM) sleep and to nightmares (Tester Dalderup 1975). Methyldopa appears to affect sleep to a less extent than the previously mentioned drugs; there was a slight prolongation of the time slept in one study (Dollery & Bulpitt 1975) but no mention is made of the quality of the sleep. Tester Dalderup (1975) lists occasional disturbing nightmares during methyldopa therapy.

3 EXTRAPYRAMIDAL SYMPTOMS

Extrapyramidal side effects of antihypertensive drugs are almost exclusively encountered in patients receiving reserpine who may display symptoms of the parkinsonian type ranging in severity from relatively mild rigidity and dyskinesia to a full-blown Parkinson's syndrome, indistinguishable from the spontaneously occuring variety (Goodwin & Bunney 1971 Tester Dalderup 1975). These cases are usually seen after large doses of reserpine and their pharmacological background is an interference of reserpine with brain dopamine metabolism (Rand & Jurevics 1977). Extrapyramidal symptoms have also been reported during methyldopa treatment but the incidence is considerably lower than after reserpine (Sweet et al. 1972). Methyldopa has actually been tried in conjunction with levodopa in parkinsonian patients (Sweet et al. 1972) but in view of the ambiguous results it is recommended that methyldopa should be avoided in patients with extrapyramidal disturbances.

4 NEUROENDOCRINOLOGICAL DISTURBANCES

Neuroendocrine effects are caused by drugs interfering with the catecholamine neurone systems controlling the release of the hypothalamic hypophyseotropic hormones or "factors" (Buckingham 1977). Among drugs used in the therapy of hypertension these central side effects are confined to reserpine and its analogues and methyldopa. Both drugs, by impairing dopamine neurotransmission in the hypothalamis cause an increase in the release of prolactin; hyperprolactinemia is apparently quite common during treatment with these drugs but it is comparatively rare that this leads to symptoms such as gynaecomastia or galactorrhea (Tester Dalderup 1975). The highly controversial issue of reserpine treatment possibly being associated with mammary cancer is aptly reviewed by Tester Dalderup (1978). Clonidine which in clinical doses does not appreciably interfere with dopamine neurotransmission has not been reported to influence neuroendocrine functions.

CONCLUSIONS

Most antihypertensive drugs cause central nervous system side effects but it is difficult to single out primary central nervous actions from those secondary to other side reactions. This is particularly evident in the case of mental symptoms such as sedation or depression. However antihypertensive agents which interfere with CNS neurotransmitter functions are clearly able to elicit primary CNS side effects. Although many of these adverse reactions may appear quite alarming to the patient, they are, with the notable exception of depressive states, rarely of a serious nature quo ad vitam. However by their subjective unpleas

anxiety these side effects frequently contribute to poor compliance with therapy and, hence, may necessitate a change in the therapeutic regimen. As indicated in the introduction, there is a regrettable paucity of quantitative data on the problem of CNS side effects of antihypertensive agents. Therefore, this field would profit from closer attention in future clinical trials of both old and new drugs, particular focus being placed on quantitation of data.

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VASOSPASTIC PHENOMENA IN PATIENTS TREATED WITH BETA ADRENOCEPTOR BLOCKING AGENTS

Keith Eliasson, Lars-Eric Lins and Kerstin Sundqvist

INTRODUCTION

Raynaud's phenomenon usually consists of episodic attacks of decreased finger circulation characterized by white fingers and paresthesias, followed by a cyanotic phase and a hyperemic phase with reddening of the skin. In some patients the cyanotic phase is absent. Half of the male patients only exhibit pallor. In about 40 per cent of all patients concomitant affection of hands and feet is seen (Hines & Christensen 1945). When a Raynaud's phenomenon exists in the absence of conditions to which it may be secondary it is called Raynaud's disease or primary Raynaud's phenomenon. It is predominantly found among younger women (sex ratio 4:1). The classical description of Raynaud's phenomenon includes induction of symptoms by cold, but some studies have failed to show an abnormal decrease in hand blood-flow after local cooling (Downey & Frewin 1973). Others have given evidence of a diminished finger blood-flow (Coffman & Cohen 1971). The pathogenesis of primary Raynaud's phenomena or Raynaud's disease is still controversial. Although a sympathetic hyperactivity has been implied as a causative factor, no hypersensitivity for norepinephrine or increased plasma contents of the substance has been proven (Coffman & Davies 1975). A decreased resting hand blood-flow but normal modulation after sympathetic release by warming, suggests an excessive sympathetic activity and rules against structural arterial disease (Peacock 1959). At least in mild cases, normal finger arteries are seen on biopsy (Coffman & Davies 1975).

During recent years, a secondary form of Raynaud's phenomenon or vasospasm has been described as a complication to treatment with beta-adrenergic receptor blocking drugs (Frohlich et al. 1969). Beta blocking drugs have worsened claudicatio intermittens in patients with a previously known peripheral arterial insufficiency but have also provoked symptoms in persons devoid of earlier signs of ischaemic vascular disease (Rodger et al. 1976). The figures given for the incidence of these side effects vary to a great extent between different authors. This may reflect differences in the active interest taken in this particular side effect and less serious vasospastic phenomena seem to be quite frequent. Zacharias (1976) made a thorough study of 390 patients treated for 6 months with propranolol. He found slightly troublesome peripheral coldness in 73 per cent of the patients who also received a diuretic. No reduction of the doses were necessary in these patients. Cases of severe Raynaud's phenomenon necessitating complete withdrawal of the drug or reduction of the dose, appeared in a frequency of only 3 per cent. This figure is in good agreement with what others have found (Table I). In contrast Marshall et al. (1976) found a very high incidence of vasospasm complicating different forms of beta-blocking therapy as compared to treatment with methyldopa, 41 and 5 per cent respectively. Beta-blocking drugs without intrinsic activity was considered to give this side effect more frequently than those with intrinsic activity or a higher degree of cardioselectivity. Vasospastic phenomena has, however, been described with different types of beta-receptor-blocking agents including cardioselective drugs. Preexisting vasospasm is thus a relative contraindication for this kind of treatment (Waal-Manning 1976). The aim of the present paper was to study the peripheral circulation in patients with va-

Table I. Incidence of vasospastic phenomena in patients treated with propranolol

Authors		Incidence %
Prichard & Gillam	(1969)	3
Tarazi & Dustan	(1972)	4
Conway	(1975)	3
Greenblatt & Koch-Weser	(1976)	6
Dalgård et al.	(1976)	0.5

Temperature measurements

The patients were studied in a sitting position at a room temperature of 23–24°C. Both hands were immersed in cold water (15°C, 15 min). The skin temperature of the pulpa of the first and third finger and the skin fold between the first and second finger were measured before cooling, immediately after 5, 10 and 15 minutes after the end of cooling. The increase in skin temperature (Δ°C) was calculated from the difference between the temperature registered 15 minutes after and immediately after the end of the cooling. The finger with the lowest skin temperature immediately after the end of the cooling was used for the measurements. When the measurements after cooling were finished the patient was placed in a supine position and vasodilated with 30–40 ml 50 per cent peroral alcohol and an abdominal heating box (40°C, 40 min). The skin temperature was measured as described above during the warming at 10, 20, 30 and 40 minutes.

Fluorescein angiography

Fluorescein angiography was performed with rapid sequence recording technique (Lund 1976).

Arterial blood pressure

Arterial blood pressure was measured in both arms with blood pressure cuff on the upper arm. The diastolic blood pressure was registered in Korotkoff phase 5. Mean arterial pressure was calculated as diastolic pressure plus one third of the pulse pressure.

Digital plethysmographic recordings

Digital plethysmographic recordings with strain gauge technique were made from the third finger of both hands for registration of the finger pulse curve and blood pressure.

Forearm blood-flow

Forearm blood-flow (ml/100 ml/min) at rest was measured by venous occlusion plethysmography with an air-filled plethysmograph placed around the forearm according to Dohn (1956) and Graf & Westersten (1959). The circulation of the hand was occluded by a cuff inflated to 150 mm Hg. The collection cuff placed around the upper arm was inflated to 50 mm Hg.

Statistical analyses were performed with Student's t-test including paired observations.

RESULTS

In all patients, disregarding treatment with selective or non-selective beta-blocker, the digital plethysmography and peripheral arterial blood pressure were normal. All patients reached a temperature of 30°C or more after 40 minutes of indirect heating suggesting a normal ability for vasodilatation. The forearm blood flow during treatment with both selective and non-selective beta-blockers was normal compared to controls (Tables III and IV).

Cardioselective beta blocking therapy (8 patients)

In all patients but one, treated with metoprolol, the skin temperature reaction after cooling was pathological, i.e. the skin temperature registered 5 minutes after the end of cooling was below 30°C. The skin temperature before cooling, the increase after cooling (Δ°C), and the forearm blood-flow were not significantly changed when terbutaline was added (Table III). Fluorescein angiography was performed in four

Table III. Skin temperature, skin temperature reaction, heart rate, mean arterial pressure, diastolic blood pressure and forearm blood-flow in eight patients during treatment with metoprolol and after addition of terbutaline

	Metoprolol	Metoprolol + terbutaline	
Skin temperature before cooling (°C)	27.2± 3.0	27.4± 3.9	n.s
Increase in skin temperature after cooling (Δ°C)	3.9± 5.1	5.1± 4.3	n.s
Heart rate (beats/min)	52 ±10	58 ± 7	p<0.05
Mean arterial pressure (mm Hg)	95 ±11	100 ±11	p<0.01
Diastolic blood pressure (mm Hg)	82 ± 9	85 ±10	p<0.05
Forearm blood flow (ml/100 ml/min)	[illegible].8± 0.8	3.7± 1.2	n

Reference values 3.8±1.3 ml/100 ml/min (Eklund et al. 1974)

sospastic phenomena before and after the addition of a beta 2 stimulant terbutaline and to discuss the possible mechanisms causing vasospasm during treatment with beta receptor-blocking agents

PATIENTS

Twenty-one patients, one female and twenty males age 53±6 years (mean±SD), developed vasospastic phenomena during treatment with beta-receptor blocking drugs. Eight patients had a previous history of myocardial infarction thirteen were hypertensives. Diagnoses WHO classification and therapy are listed in Table II. No clinical signs or previous histories of collagenous disease were registered. All patients had a normal sedimentation rate and plasma electrophoresis. They had no anemia, leucopenia, antinuclear factors or cryoglobulins. Fasting blood glucose was normal and no patient had glucosuria. Thirteen patients were smokers. Thirteen patients were treated with a cardioselective drug and eight with a non-selective one. Half of the patients also received other drugs but this treatment was held constant during the study (Table II).

On an average the vasospastic symptoms appeared after two months of treatment. The most common complaints were cold and white fingers with decreased sensibility. One third of the patients reported symptoms even when staying indoors. Peripheral cyanosis and paresthesias were found in six patients. In many cases intense active rewarming of the hands was required for relief of the symptoms. Four patients had a previous history of cold hands one also suffered from migraine. Seven patients experienced cold feet, but none had claudicatio intermittens.

METHODS

The patients were examined before and 3 weeks after adding terbutaline to the beta-blocker therapy which was held constant during the study. All investigations were performed in the morning. The patients had taken their regular morning dose of medicine before arriving at the laboratory. They were requested not to drink coffee or tea or smoke for 4 hours before the test.

Table II. Diagnoses, WHO classification and therapy in twenty-one patients with vasospasm during treatment with beta-blocking drugs

Patient no	Diagnosis	WHO group	Beta-blocking therapy	Daily dose mg	Other drugs
1	Primary hypertension	I	metoprolol	200	hydrochlorthiazide
2	Primary hypertension	I	metoprolol	200	–
3	Primary hypertension	I	metoprolol	200	hydralazine, hydrochlorthiazide
4	Primary hypertension	II	metoprolol	200	–
5	Hypertension chronic glomerulonephritis	II	metoprolol	200	
6	Primary hypertension	I	metoprolol	400	hydrochlorthiazide
7	Primary hypertension	I	metoprolol	400	–
8	Primary hypertension	I	metoprolol	400	hydrochlorthiazide
9	Primary hypertension	I	propranolol	80	bendroflumethiazide, dipyridamole
10	Hypertension, chronic glomerulonephritis	I	propranolol	240	hydralazine
11	Primary hypertension	I	timolol	10	
12	Primary hypertension	I	timolol	20	hydralazine, hydrochlorthiazide
13	Primary hypertension	III	timolol	20	–
14	Myocardial infarction		metoprolol	100	furosemide, hydrochlorthiazide
15	Myocardial infarction		metoprolol	100	digoxin
16	Myocardial infarction		metoprolol	100	furosemide
17	Myocardial infarction		metoprolol	150	digoxin
18	Myocardial infarction		metoprolol	150	furosemide
19	Myocardial infarction		alprenolol	150	–
20	Myocardial infarction		alprenolol	400	digoxin
21	Myocardial infarction		alprenolol	400	

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Forearm blood flow (ml/100 ml/min)	2.8± 0.8	3.7± 1.2	n.s.

Reference values 3.8±1.3 ml/100 ml/min (Eklund et al. 1974)

Table IV Skin temperature, skin temperature reaction heart rate, mean arterial pressure, diastolic blood pressure and forearm blood-flow in six patients during treatment with a non-selective beta-blocker and after addition of terbutaline

	Non-selective beta-blocker	Non-selective beta-blocker + terbutaline	
Skin temperature before cooling (°C)	26.8± 4.2	29.4± 4.4	n.s.
Increase in skin temperature after cooling (Δ°C)	9.4± 4.5	5.9± 4.6	n.s.
Heart rate (beats/min)	58 ±10	56 ±11	n.s.
Mean arterial pressure (mm Hg)	107 ±12	103 ± 6	n.s.
Diastolic blood pressure (mm Hg)	93 ±13	91 ± 7	n.s.
Forearm blood-flow* (ml/100 ml/min)	3.2± 1.3	3.2± 1.5	n.s.

Reference values 3.8±1.3 ml/100 ml/min (Eklund et al. 1974)

of the patients during treatment with metoprolol and after addition of terbutaline. The appearance time decreased from 24±6 seconds (mean±SD) to 20±4 seconds. Reference values 12–15 seconds (Pernow – to be published). No statistical analyses were made.

Non-selective beta blocking therapy (5 patients)
In all patients treated with a non-selective drug, the skin temperature reaction after cooling was pathological i.e. the skin temperature registered 5 minutes after the end of cooling was below 30°C. The skin temperature before cooling, the increase after cooling (Δ°C) and the forearm blood flow was not significantly changed when terbutaline was added (Table IV). The heart rate the mean arterial pressure and the diastolic blood pressure was also unchanged after the addition of terbutaline (Table IV)

DISCUSSION

Our patients have shown symptoms of vasospasm ranging from increased preexisting peripheral coldness to development of classical *Raynaud's phenomena*. In some cases severe vasospasm has occurred even without provocation by cold. There seems to be no relation between the degree of blood pressure reduction and the occurrence of symptoms. Several facts support our view that the vasospastic complaints were caused by the beta-blocker therapy. As stated above *primary Raynaud's disease* shows a female predominance. In our material the reverse was true. The incidence of smoking was comparable to the population in general. Other forms of secondary Raynaud's phenomena were excluded with reasonable certainty. In some patients a reduction of the dose gave some relief of the symptoms and whenever medication was withdrawn the vasospastic phenomena were abolished or brought back to the preexisting level.

Beta-blocking agents decrease cardiac output and may thereby deteriorate the peripheral circulation particularly in patients with a previously diminished blood flow of the extremities. Julius et al (1972) have conveyed the hypothesis that the reduction of the blood volume after intravenously administered propranolol would depend on a blockade of a tonic dilatation of small blood vessels mediated by beta adrenergic receptors. A diminished circulating blood volume would then cause impairment of the peripheral circulation. *Established hypertension is characterized by* a normal cardiac output but an elevated total peripheral resistance. After acute administration of propranolol cardiac output is decreased but blood pressure is maintained because of an elevation of vascular resistance. After long-term treatment cardiac output is still decreased but to a smaller extent and the peripheral resistance readjusts towards the initial value (Hansson et al 1974). After chronic antihypertensive therapy a partial normalization of peripheral resistance after maximal vasodilatation has been found indicating reversibility of *structural abnormalities (Sivertsson & Hansson 1976)*. In our own patients finger pulse curves, blood pressures and ability of vasodilatation were all normal indicating the absence of organic lesions. *The forearm blood flow was normal in all patients during beta-blocker therapy.* This suggests that the flow decrease was localized to the skin and subcutaneous tissue of the peripheral parts of the limbs

and may imply that a decreased cardiac output did not contribute to any significant extent to the peripheral vasospasm.

Another plausible explanation for Raynaud's phenomena in patients on beta-blockers is a primary effect on the receptors in the peripheral vascular system. The receptor theory by Lands et al. (1967) has been modified after the finding that differential blockade pattern were produced in the cat heart using different receptor agonists and antagonists (Carlsson et al. 1972). This finding has later been confirmed in human atria (Åblad et al. 1974) and guinea pig bronchi (Furchgott & Wakade 1975). Carlsson et al. (1972) suggested that these findings are best explained by the hypothesis that both beta-1 and beta-2 receptors coexist in the same tissue and mediate the same response. The proportions between these receptors might vary from tissue to tissue and also between individuals from the same species. The highly cardioselective drugs has induced severe bronchospasm in some patients. According to Wall-Manning & Simpson (1971), this could be explained by assuming that beta-1 receptors are of great importance for mediating relaxation of bronchial smooth muscle in these very patients.

As stated above some evidence exists for different types of beta-receptors mediating vasodilatation in different tissues. This, in turn, might explain the occurrence of peripheral vasospasm among patients treated with a cardioselective beta-blocker assuming the existence of predominantly beta-1 receptors in their skin vessels. In a recent thesis, Belfrage (1978) showed the existence of beta-1 receptors in subcutaneous vessels mediating vasodilatation. It is not known if derangements of the subcutaneous circulation can cause Raynaud's phenomena. Different therapeutic measures for Raynaud's phenomena have mainly consisted of attempts to influence the sympathetic nervous system. Good results have been reported after local sympathectomy (Gifford et al. 1958) and after treatment with alpha-receptor-blocking substances (Taylor et al. 1965). Naesa (1973) described a patient with bronchial asthma who was cured from a Raynaud's phenomenon by treatment with terbutaline, a highly selective beta-2 receptor agonist. When given as a single drug it produces a compensatory tachycardia and an increase in cardiac output (Arner et al. 1970). The peripheral resistance is substantially decreased (Sackner et al. 1975). Both primary and secondary Raynaud's phenomena have been successfully treated with terbutaline (Zabel et al. 1974) but the effect has tended to be of short duration (Thune & Fyrand 1976).

In combination with propranolol in spontaneously hypertensive rats, terbutaline had no effect on blood pressure whereas the combination with metoprolol resulted in a significant blood pressure reduction (Malmstray et al. 1977). The probable interpretation of this finding is that only metoprolol could allow peripheral vasodilatation mediated by beta-2 receptor stimulation. Andersson & Berglund (1975) could not confirm an additive blood pressure effect in patients after adding salbutamol to previous practolol treatment. In our patients, a significant increase in calculated mean arterial pressure when adding terbutaline to the treatment with a cardioselective drug was found. In patients treated with non-selective drugs the mean arterial pressure was unchanged. This is taken as evidence for a remaining ability to dilate peripheral vessels and increase cardiac output in patients on cardioselective drugs. The increase in calculated mean arterial pressure still remains unexplained. The forearm blood flow, however, showed no significant increase after the addition of terbutaline. An increase in heart rate was found in patients treated with metoprolol. The absence of tachycardia during active warming suggests a blockade of cardiac beta-receptors, but does not seem to exclude the possibility of a reflex increase in heart rate following vasodilatation after terbutaline.

After the addition of terbutaline the temperature reaction to local cooling did not show any significant improvement. In a few patients, however, the appearance time of fluorescein decreased suggesting increased skin blood-flow. It is too early to state whether this could be due to methodological factors only or to a reflection of a true non-responsiveness to the beta-stimulant. The hypothesis of a different receptor population in patients with vasospasm cannot yet be examined because we still lack definite data from our prospective study and from provocation tests.

Another explanation for the somewhat paradoxical reaction of vasospasm on selective beta-blockers might be an increased sensitivity to blockade in the beta-2

receptors of these patients Metoprolol has a fifty fold increased affinity for beta 1 receptors compared to beta 2 receptors (Åblad et al 1973) but assuming a different sensitivity one might encounter a different response. A deficient beta 2 receptor might be blocked even by the weak action of a cardioselective agent and the ensuing alpha-adrenergic dominance could then cause the vasospasm A number of studies have given evidence for different peripheral actions of cardioselective and non-selective beta blockers. Åblad et al (1973) studied haemodynamic effects in conscious dogs and found that propranolol and metoprolol had the same lowering effect on cardiac output and no blood pressure reducing action because of a reflex vasoconstriction. However during epinephrine infusion only propranolol gave rise to an increase in blood pressure because of beta 2 receptor blockade. Johnsson (1975) made similar findings in human volunteers. This difference in peripheral action between different types of beta blockers was confirmed after long term oral treatment at rest (van Herwaarden et al 1977) and acutely during isometric exercise (Sangvik et al 1976). In patients who had developed vasospastic side effects during treatment with non-selective drugs Marshall et al (1976) found improvement after changing to a drug with a higher degree of intrinsic activity and Waal Manning (1976) recommends changing the therapy from non selective to cardioselective drugs in angina patients with symptoms of peripheral coldness. Hansson et al (1976) studied side effects during long term treatment with atenolol In 94 patients with this drug only one case of Raynaud's phenomenon and 4 cases of cold extremities were found.

In conclusion, many different theories could be delivered to explain why vasospastic phenomena occur during treatment with beta-adrenergic-receptor blocking drugs. Several studies indicate that an alpha-adrenergic sympathetic dominance can give disturbances in the peripheral haemodynamics, probably by the elimination of the ability of beta-2 mediated vasodilatation. It is, however still unknown if this could affect the skin circulation and temperature regulation. Vasospastic phenomena arise after treatment with both non-selective and cardioselective drugs Quantitative differences might exist, but this question, like that of the origin of the phenomenon remains to be definitely answered Clinically it would be advisable to prescribe beta-blocking drug cautiously to patients with preexisting signs of peripheral vascular disease.

SUMMARY

Twenty-one patients developed Raynaud's phenomenon during treatment with beta-adrenoceptor blocking agents. The vasospastic symptoms were obviously related to the treatment, but their pathogenesis is still controversial A decrease in cardiac output might explain the phenomenon According to our very preliminary data an alpha-adrenergic dominance caused by a direct effect on the peripheral circulation seems more probable. Vasospastic symptoms may arise after treatment with both cardioselective and non-selective beta blocking agents. Cautious prescription of beta blocking drugs to patients with preexisting peripheral vascular disease is recommended

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KIDNEY DAMAGE INDUCED BY ANTIHYPERTENSIVE TREATMENT

Nils C. Henningsen

The frequency of patients with severe essential hypertension who demonstrate progressive impairment of kidney function during treatment is high. The main reason for that is an imperfect control of the blood pressure. Side-effects from the pharmacological treatment play only a limited role. It is now generally accepted that even patients with renal hypertension with or without renal insufficiency only get benefits of pharmacologically induced normotension (Wilson 1953, Pettinger 1976, Bengtsson et al. 1968). The kidney damage may be severe (creatinine > 400 µmol/l) and the glomerulus filtration rate decreasing despite normotension, but the cardiovasculary system is more or less protected demonstrated by a lower frequency of vascular catastrophes (Veterans Administration 1967, 1970).

The above mentioned sentences does not mean that negative effects on renal function during antihypertensive treatment do not exist, but the problem has, however, a limited clinical impact. During the last ten years only eight reports of untoward side-effects from the kidneys have been reported to the Swedish Board for Drugs side-effects (Table I) and some of these are probably not related to the suspected drug.

This report is only dealing with published or own experience of negative effects on kidney function and only drugs who are used today are discussed.

PATIENTS WITH NORMAL RENAL FUNCTION

More than 80% of all hypertensive patients can be referred to this group.

Thiazides

Treatment with thiazides for hypertension is widespread all over the world and some reports of kidney damage have occurred (Lyons et al. 1973, Muehrcke & McMillan 1963, Kjellbo et al. 1965, Dodds & Foord 1970, Fitzgerald 1960). Some of these have been quite specific as the few reported cases of renal necrotizing vasculitis (Kjellbo et al. 1965) or allergical interstitial nephritis (Lyons et al. 1973) which in most cases have

Table I. All untowarded side-effects from the urogenital system during antihypertensive treatment recorded at the Swedish Board for Drug side-effects

Drug and dosage		Symptoms	Drug related
Inderal (propranolol)	20 MG 4	oliguria	++
Inderal (propranolol)		pollakisuria	+++
Inderal (propranolol)	40 MG x 2	hematuria + hemospermia	+
Dichlotride (hydrochlorothiazid)	90 MG 1	proteinuria	+
Hygroton (chlortalidone) + Apresolin (hydralazin)	50 MG x 1 + 10 MG 3	urinary retention	+
Midamor (amiloride) + Lasix (furosemide)	5 MG 1 40 MG 1	increase of creatinine (200–400 µmol/l) nausea	++
Esidrex-K (hydrochlorothiazide) Moduretic (hydrochlorothiazide, amiloride)	25 MG x 1 50 MG x 1 5 MG x 1	hemospermia increase of creatinine	+++

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ing agents: atenolol pindolol propranolol and metoprolol After a run-in period the patients were given the drugs in random order each period lasting for four weeks. The serum TG concentration was increased significantly during treatment with all these beta adrenoceptor blocking drugs and the per cent increase of the serum TG concentration varied between 25% and 63% The serum cholesterol concentration remained unchanged

THE OSLO STUDY

In a study of hypertensive patients the basic treatment was 50 mg hydrochlorothiazide per day If the blood pressure was not normalized 0 5–1 5 g of α methyl dopa was added If the patients had intolerable side effects during this treatment therapy was shifted and instead 80–320 mg propranolol per day was given Patients were treated for a period of 3 years. Patients on hydrochlorothiazide + α methyldopa did not exhibit any significant changes of the serum lipid concentrations. However patients on hydrochlorothiazide + propranolol had a mean serum TG concentration elevation from 1 87 to 2 45 mmol/l ($p < 0\,01$). The serum cholesterol concentration remained unchanged

THE GOTHENBURG STUDY

In the Gothenburg study Berglund (1978) treated men for 4 years with either bendroflumethiazide (Salures-K) or propranolol (Inderal). Whole serum cholesterol was significantly reduced during treatment with both these drugs whereas men on propranolol demonstrated a significant increase of the TG fraction from 1.8 to 2.3 mmol/l (28% $p \leq 0\,001$). The data do not permit an analysis in what lipoprotein fraction the cholesterol reduction took part. However since VLDL TG increased it is most likely that the reduction of cholesterol might have occurred in the HDL fraction, which is inversely correlated to the VLDL concentration.

MECHANISMS OF LIPOPROTEIN METABOLISM DISTURBANCE

Several studies have thus indicated that beta-adrenoceptor blocking agents and diuretics may cause considerable changes in the serum lipid and lipoprotein pattern. A summary of these studies is shown in the Table I What are the possible mechanisms leading to these changes?

The beta-adrenoceptor blocking effect on lipolysis

Table I. Serum lipid changes after treatment with antihypertensive drugs. Statistically significant differences are shown in % and significance is indicated as $p < 0\,05$ $p < 0\,01$ and ** $p < 0\,001$ (ns = no significance)

Author	Treatment duration	Antihypertensive therapy	TG	Cholesterol
Ames & Hill (1976)	3 months	diet + chlorthalidone	+26%***	+5%**
Berglund (1978)	4 years	Bendroflume-thiazide	+13%**	−9%***
		Propranolol	+28%***	−7%***
Waal Manning (1976)	1 year	Metoprolol	+37%**	ns
Nilsson (1977)	3 months	Metoprolol	ns	ns
Shaw (1978)	1 month	Atenolol	+62%	ns
		Pindolol	+28%	ns
		Propranolol	+37%	ns
		Metoprolol	+25%	ns
Helgeland (1978)	3 years	Hydrochlorothiazide + methyldopa	ns	
		Hydrochlorothiazide + propranolol	+31%**	ns
Tanaka (1976)	2 months	Propranolol	ns	ns
			(VLDL TG+49%**	
			apo-HDL	−20%**)

and FFA release in the acute situation does not eliminate the possibility that an overshoot occurs when the effect of the drug has diminished or disappeared. The study of Tanaka et al (1976) in fact demonstrates that increased FFA concentrations may be observed after long-term treatment with propranolol.

Another hypothetical explanation for the increase of the TG concentration is an impaired elimination of TG in peripheral tissues. Barboriak and co-workers (1973) demonstrated that after two weeks treatment with propranolol the clearing time after a fatty meal had increased significantly.

LIPOPROTEIN DIFFERENCES

Almost all of the studies referred to have only dealt with whole serum lipid analyses. What do these changes correspond to in terms of lipoprotein concentrations

An increase of total serum TG concentration with unchanged or even lowered total cholesterol concentration is most likely the result of the following metabolic development (Figure 1): The increase of total serum TG concentrations is generally a reflection of an increase of the VLDL TG concentration since the TG concentration in the LDL and HDL lipoprotein fractions are of minor importance from a quantitative point of view and vary little. When the VLDL TG concentration increases, the cholesterol concentration will also increase in proportion, since the TG/cholesterol ratio in this fraction is fairly constant under these circumstances. Furthermore, there is a negative relationship between the VLDL concentration and the HDL concentration, well established from several previous studies. As consequence of the VLDL increase the HDL concentration is lowered (Carlson 1978)

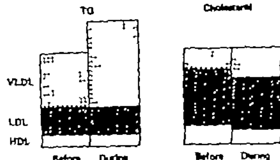


Figure 1. Hypothetic: Serum lipoprotein changes after treatment with diuretics or beta-adrenoceptor blocking agents.

The fact that total cholesterol remains unchanged in many of the studies cited above can thus be explained by the combination of an increase of VLDL cholesterol and a concomitant reduction of similar magnitude of HDL cholesterol. As a result of these changes the patient has now developed a hypertriglyceridaemia with lowered HDL concentrations. Both an increase of the VLDL TC concentration and the lowered HDL concentration are factors which carry increased risks for development of atherosclerotic manifestations. Thus the metabolic alteration induced by the antihypertensive treatment could have unfavourable effects on serum lipoprotein concentrations and composition. Shaw et al. (1978) conclude their paper with the following comment: *If plasma triglyceride levels remain elevated during long term treatment of hypertension with beta-adrenoceptor antagonists, do the benefits outweigh the risks?"*

In Table I the reviewed studies are compiled

It seems obvious from this review that there is a great need for long-term studies of the effects of *antihypertensive treatment* on lipoprotein metabolism in patients with elevated blood pressure. In order to achieve this, lipoprotein analyses are indispensable.

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NEGATIVE CONSEQUENCES OF REDUCTION OF BLOOD PRESSURE – INFLUENCE ON SEXUAL FUNCTION

Rune Sannerstedt

Although it has long been known that treatment with antihypertensive drugs may have an adverse effect on sexual function, and these side effects have been a common phenomenon ever since the days of the ganglion blockers, the otherwise so voluminous hypertension literature contains little information on this point. This is perhaps not surprising, bearing in mind the fact that this is still regarded as a delicate area by both patients and doctors, but nevertheless it is regrettable that the available information does not provide an adequate basis for analysis of this problem, which is often a decisive factor for the individual patient. What is more, the literature deals almost exclusively with the sexual situation of the male patient. Women seem to have been forgotten in this context and it is symptomatic that the Australian author Bell, in his comprehensive review "Autonomic nervous control of reproduction: Circulatory and other factors" includes a section entitled "Clinical implications of male sexual function" but omits a corresponding analysis of female sexual function (Bell 1972). Some years later another two Australian authors conclude resignedly that "It is of interest that most attention to side effects of drugs in female sexual behaviour has focused on an exclusively female-orientated preparation, the oral contraceptive pill" (Dennerstein & Burrows 1977).

BRIEF BACKGROUND TO THE BASIC PHYSIOLOGY OF SEXUAL FUNCTION

Both the sympathetic and parasympathetic nervous systems are involved in the sexual act. In the male the autonomic activation leads to erection of the penis and mucus secretion and in the female to hyperaemia of the vulva and vagina, as well as mucus secretion. In general, mental stimulation increases sympathetic activity while local stimulation leads to increased parasympathetic activity. Ejaculation and orgasm are governed by sympathetic nervous impulses which cause rhythmic peristalsis in the genital passages.

SPONTANEOUS DISTURBANCES OF SEXUAL FUNCTION

When assessing the possible association between antihypertensive medication and disturbances of sexual function it is important to bear in mind that both impotence and frigidity occur spontaneously with high frequency. It has been reported that about half of all men, when directly questioned, state that they are dissatisfied with their sex lives (Lording 1978). The prevalence of impotence increases with increasing age and Lording states it to be 75% in men above the age of 60. Using a questionnaire, Bulpitt et al. (1976) found that the frequency of impotence in men with untreated hypertension was 17%, which may be compared with the figure of 7% in their normal controls. While failure of ejaculation did not occur at all in the control group, 7% of the untreated hypertensive men complained of this. The frequency of coitus did not differ between the groups. Typically, the report contains no information about the corresponding situation in female patients, despite the fact that women accounted for more than 50% of the population studied.

INFLUENCE OF HYPOTENSIVE DRUGS ON SEXUAL FUNCTION

Bulpitt et al. (1976) also investigated the frequency of impotence and failure of ejaculation in treated hypertensive men and found higher frequencies (25% and 26%, respectively) compared to untreated hypertensive men and normal controls. *Secondary impotence*, i.e. failure of erection in men who had previously been able to achieve coitus, was formerly a frequent phenomenon during treatment with *ganglion blocking drugs*. This side effect may also occur with other sympathetic inhibitors, such as bethanidine, gua-

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DISCUSSION

Calle Bengtsson

As a complement to this paper I would like to describe what has happened to women receiving ß-blockers and diuretics respectively in the population sample we are presently studying in Gothenburg. About 39 women have during the six year period between the studies 1968–1969 and 1974–1975 been put on diuretics and roughly 50 women have in the meantime been placed on ß-blocking therapy We have compared the total number of women examined at both occasions. There was no change in total cholesterol levels neither in those receiving diuretics nor in those treated with ß-blockers although some increase was noted in the whole material With regard to triglycerides we observed an increase of 0 1 mmol/l in the whole material and an increase of 0.35 mmol/l in those given ß-blockers, i e a change of 0 25 mmol/l with a possible slight decrease of 0 1 mmol/l in those receiving ß-blockers.

Stephan Rössner

Were there any fluctuations in body weight in these women?

Calle Bengtsson

All changes in body weight were similar in the various groups.

Keith Eliasson

At the Ninth Nordic Hypertension Meeting in April 1978 preliminary data from the Oslo survey dealing i.a. with the HDL fraction were presented. Significantly lower values were observed in patients treated with the combination hydrochlorothiazide + propranolol when compared to similar groups given hydrochlorothiazide alone or in combination with methyl dopa. Body weight was stable during three years but diet or smoking habits were not checked.

NEGATIVE CONSEQUENCES OF REDUCTION OF BLOOD PRESSURE – INFLUENCE ON SEXUAL FUNCTION

Rune Sannerstedt

Although it has long been known that treatment with antihypertensive drugs may have an adverse effect on sexual function, and these side effects have been a common phenomenon ever since the days of the ganglion blockers, the otherwise so voluminous hypertension literature contains little information on this point. This is perhaps not surprising, bearing in mind the fact that this is still regarded as a delicate area by both patients and doctors, but nevertheless it is regrettable that the available information does not provide an adequate basis for analysis of this problem, which is often a decisive factor for the individual patient. What is more, the literature deals almost exclusively with the sexual situation of the male patient. Women seem to have been forgotten in this context and it is symptomatic that the Australian author Bell in his comprehensive review "Autonomic nervous control of reproduction: Circulatory and other factors" includes a section entitled "Clinical implications of male sexual function" but omits a corresponding analysis of female sexual function (Bell 1972). Some years later another two Australian authors conclude resignedly that "It is of interest that most attention to side effects of drugs in female sexual behaviour has focused on an exclusively female-orientated preparation, the oral contraceptive pill" (Dennerstein & Burrows 1977).

BRIEF BACKGROUND TO THE BASIC PHYSIOLOGY OF SEXUAL FUNCTION

Both the sympathetic and parasympathetic nervous systems are involved in the sexual act. In the male the autonomic activation leads to erection of the penis and mucus secretion and in the female to hyperaemia of the [illegible] and vagina, as well as mucus secretion. In general, mental stimulation increases sympathetic activity while local stimulation leads to increased parasympathetic activity. Ejaculation and orgasm are governed by sympathetic nervous impulses which cause rhythmic peristalsis in the genital passages.

SPONTANEOUS DISTURBANCES OF SEXUAL FUNCTION

When assessing the possible association between antihypertensive medication and disturbances of sexual function it is important to bear in mind that both impotence and frigidity occur spontaneously with high frequency. It has been reported that about half of all men, when directly questioned, state that they are dissatisfied with their sex lives (Lording 1978). The prevalence of impotence increases with increasing age and Lording states it to be 75% in men above the age of 60. Using a questionnaire, Bulpitt et al. (1976) found that the frequency of impotence in men with untreated hypertension was 17%, which may be compared with the figure of 7% in their normal controls. While failure of ejaculation did not occur at all in the control group, 7% of the untreated hypertensive men complained of this. The frequency of coitus did not differ between the groups. Typically, the report contains no information about the corresponding situation in female patients, despite the fact that women accounted for more than 50% of the population studied.

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nethidine, methyldopa, clonidine and reserpine. Thus, *Bulpitt & Dollery (1973)* reported impotence in 67% of men treated with bethanidine and 54% of men treated with guanethidine. Patients treated with diuretics or spironolactone may also occasionally complain of this symptom. *Failure of ejaculation* is above all a characteristic side effect of ganglion blocking agents but may also occur with other sympathetic inhibitors. Thus Bulpitt & Dollery (1973) reported failure of ejaculation in six out of 10 men with guanethidine and in 7 out of 17 treated with bethanidine. *Retrograde ejaculation* caused by paralysis of the internal bladder sphincter may occur during treatment with postganglionic sympathetic inhibitors such as bethanidine and guanethidine, leading to what has been called "dry run". As already indicated *frigidity* and *failure of orgasm* in women during antihypertensive treatment does not seem to have been studied in any detail. It may however be assumed on good grounds that antihypertensive drugs cause disturbances of sexual function in women too.

FINAL COMMENT

In view of the possible serious consequences of disturbance of sexual function for the individual and his or her social life, this side effect of antihypertensive drugs merits closer attention than it has probably received up to now. This may be achieved by actively questioning patients treated with these drugs concerning changes in their sex lives and if evidence of disturbance of sexual function is found adapting the treatment accordingly. This can probably best be achieved by altering the patient's medication rather than by intermittent withdrawal of suspected antihypertensive drugs, e.g. over the weekend as has been suggested by British authors.

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DISCUSSION

Stephan Rössner

At The Annual General Meeting of the Swedish Society of Medical Sciences 1977 we reported the results of a questionnaire to about 50 post myocardial infarction patients, attempting to evaluate their sexual situation with regard to possible changes after the infarction and concomitant drug intake. About a third of these patients were treated with ß-receptor blocking drugs. Our questionnaire did not reveal any drug-related alterations in the quality of sexual life (Nilsson & Rössner 1978).

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FETAL EFFECTS OF ANTIHYPERTENSIVE DRUGS

Per Lundborg

This presentation will be very brief and concentrate on a few points of general interest.

First, most doctors and pregnant women in our country are today extremely well aware of the potential hazard for the fetus if the mother is treated with various drugs during pregnancy at least during the first trimester. Therefore, the question often is raised, whether the optimal treatment for the mother has to be withheld in favour of the fetus, or if the mother should be treated, thereby risking adverse effects on the fetus.

It has to be stated, I think, that in many situations the best for the fetus as well as for the mother is an adequate treatment of serious disease.

Secondly I would like to point out that the placenta cannot be considered an organ whose prime function is to protect the fetus against injury and infection, providing a physical barrier to the passage of noxious substances from mother to fetus.

In this sense the term "placenta barrier" must be considered a myth. It seems unlikely that a living cell membrane could be absolutely impermeable to a given compound. On the contrary it is now believed that any substance found in the maternal or fetal blood should be able to penetrate the placenta to some extent unless it is destroyed or altered during passage (Moya & Thorndike 1962).

The important question is not whether a given substance does or does not pass the so-called placenta barrier but the rate and mechanism of transfer involved.

THE TRANSPORT MECHANISMS

The basic mechanism by which substances may cross the placenta are the same as those of other biological membranes; they have been reviewed in detail by several authors (e.g. Page 1957, Moya & Thorndike 1962, Ginsburg 1971). They may be considered as with other natural membranes, under four main headings – simple diffusion, facilitated diffusion, active transport and special processes. Only simple diffusion and active transport will be briefly considered here.

Simple diffusion

In this instance substances cross the placenta from regions of higher to lower concentration so as to equal the concentrations on either side of the barrier.

The rate at which placental transfer occurs by these means is thought to be governed by standard physicochemical considerations. One would therefore expect the passage of lipid soluble substances across the placenta to be accelerated compared with those that are less fat soluble.

Active transport across a membrane

This implies molecular transfer against an electrochemical gradient and must entail the expenditure of metabolic energy. This mechanism is responsible for the transfer of vitamins, amino acids, and essential ions such as calcium from mother to the fetus. Amino acid analogues like α-methyl-dopa, can similarly be expected to utilize this mechanism and also to compete with other amino acids for transfer sites.

Irrespectively of the transport mechanism utilized most pharmacologically active compounds given to the mother passes from the mothers blood to the fetal blood.

At acute drug administration the rate of transfer determines the maximal drug concentration reached in the fetal blood. At drug administration for a long period, as is the case in antihypertensive therapy also drugs passing at a very slow rate can be expected to reach high concentrations in the fetal blood.

MORPHOLOGIC AND FUNCTIONAL EFFECTS ON THE FETUS

Drug effects on the fetus are of two major types. Early in pregnancy during formation of the organ systems, the primary concern is morphologic abnormalities (i.e. congenital anomalies). Later in pregnancy functional considerations are of greater significance and during delivery such factors as respiratory depression of the neonate and inability of the neonate to metabolize or eliminate. It should also be pointed out that although the formation of most organ systems is completed after the first trimester a vast number of neural pathways in the brain are not fully developed until late in pregnancy or after birth. The possibility has to be considered that drugs interacting with brain neurotransmission can interfere with the final development of brain transmitter systems. For example continuous treatment with dopamine receptor blocking agents during the period of rapid development of brain dopamine systems has been found to result in persistent behavioural and biochemical brain changes in the rat (Ahlenius et al 1973 Engel & Lundborg 1974). This fact has to be considered in the choice of antihypertensive therapy during pregnancy.

ANTIHYPERTENSIVE AGENTS

Various groups of antihypertensives are listed in Table I. Although thiazide diuretics given to the mother occasionally can induce trombocytopenia postnatally this effect is generally reversible, and many physicians consider diuretics the first drug to be used in pregnancy hypertension.

Table 1 Anti-hypertensive agents

1. Diuretics
2. Sympathetic inhibitors
   a) Central effect clonidine, methyldopa
   b) Ganglionic blocking agents
   c) Agents interfering with granular storage mechanisms: Reserpine, bethanidine, guanethidine
   d) Adrenergic receptor blocking agents: Alpha-blockers, beta-blockers, Non-selective, selective
3. Vasodilators: Hydralazine

Clonidine and α methyl-dopa both interfere with central adrenergic mechanisms. Although nothing has been published about harmful fetal effects of these drugs in humans these drugs could theoretically be expected to interfere with the development of adrenergic mechanismus in the brain. Ganglion blocking drugs are only of minor interest in the treatment of hypertension today. It deserves to be mentioned however that ganglion blockade in the neonatal period has been found to interfere with the development of postsynaptic neurons in the rat (e.g. Black & Geen 1973).

OTHER ANTIHYPERTENSIVE AGENTS

Concerning reserpine bethanidine and guanethidine, they all interfere with amine storage mechanisms in adrenergic neurons. It has been argued that bethanidine and guanethidine do not pass the placenta membranes due to low lipid solubility. This does not seem very probable (see above). All three drugs can be expected to interfere with the development of adrenergic mechanisms.

BETA BLOCKING AGENTS

Beta-blocking drugs are not seldom used in pregnancy. There are som publications available suggesting that treatment with a non-selective beta-blocker propranolol may have resulted in a small placenta, intrauterine growth inhibition and postnatal hypoglycemia and bradycardia (Fiddler 1974 Gladstone et al 1975). If these effects, at least in part, can be related to beta receptor blockade it is possible that they may be avoided by using a selective beta-blocker (Sandstrom 1978).

In addition to the intrauterine effect of beta-blockers pediatricians have pointed out that betablockade during delivery might deprive the newborn child of the possibility to respond to hypoxic situations with increased heart rate (Kjellmer personal communication).

HYDRALAZINE

Hydralazine, finally has been in clinical use for many years. No reports exist to my knowledge about any adverse effects on the fetus, associated with hydralazine treatment during pregnancy.

CONCLUSIONS

In conclusion, all drugs given to the pregnant woman for the treatment of hypertension can be expected to pass the placenta membranes and reach about the same concentration in the fetal blood as in the mother's blood. It is the author's personal view that drugs interfering with neurotransmission centrally or peripherally should be used with caution and if possible be avoided.

Thiazides and hydralazine can probably be considered relatively safe drugs. If beta-blockers are to be used beta-1 selective drugs should be preferred.

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DISCUSSION

Mats Hemming

I would like to have your opinion about the placental transfer of bethanidine and guanethidine since these drugs are poorly absorbed from the gut and are said not to pass the blood-brain barrier

Per Lundborg

This is true also of skeletal muscle relaxants like curare but there are reports of muscular paralysis in children delivered by mothers treated with curare-like drugs for tetanus In my opinion placental transfer is only a question of time

Hans Lindholm

We have determined serum levels of atenolol in 7 pairs of mothers and children, umbilical blood samples were taken immediately post partum There were no significant differences in atenolol levels between or within pairs We have also examined hydralazine under similar conditions in 5 pairs, observing a higher concentration in the child than in the mother In one patient receiving hydralazine 150 mg daily significant concentrations of the drug were found in breast milk.

Mats Hemming

It has been said that atenolol does not appreciably pass membranes of the placental or blood-brain barrier type but this would appear not to be true in the long term situation.

Per Lundborg

It might be noted that mother and infant have different degrees of [illegible]

MORPHOLOGIC AND FUNCTIONAL EFFECTS ON THE FETUS

Drug effects on the fetus are of two major types. Early in pregnancy during formation of the organ systems, the primary concern is morphologic abnormalities (i.e. congenital anomalies). Later in pregnancy functional considerations are of greater significance, and during delivery such factors as respiratory depression of the neonate and inability of the neonate to metabolize or eliminate. It should also be pointed out that although the formation of most organ systems is completed after the first trimester a vast number of neural pathways in the brain are not fully developed until late in pregnancy or after birth. The possibility has to be considered that drugs interacting with brain neurotransmission can interfere with the final development of brain transmitter systems For example continuous treatment with dopamine receptor blocking agents during the period of rapid development of brain dopamine systems has been found to result in persistent behavioural and biochemical brain changes in the rat (Ahlenius et al 1973 Engel & Lundborg 1974) This fact has to be considered in the choice of antihypertensive therapy during pregnancy

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TREATMENT OF HYPERTENSION – RISK/BENEFIT EXCERPTS OF A PANEL DISCUSSION

Chairman and referee: Hans Dunér
Panel members: Lennart Hansson, Mats Henning, Rune Sannerstedt and Hans Åberg

There is general agreement that arterial hypertension is an important risk factor for the development of ischaemic heart disease, cerebrovascular disease and renal insufficiency. With increasing levels of blood pressure the morbidity and mortality from these conditions increase and the negative effect of raised arterial pressure can be observed already in young adults. These conclusions are based on studies such as The Build and Blood Pressure Study (1959), The Framingham Study (Kannel et al. 1970), and The Chicago Stroke Study (1974).

As regards the prophylactic effect of antihypertensive treatment on cardiac complications both the Veterans Administration Trials (1967–1970) and The Framingham Study (Kannel et al. 1970) have demonstrated that development of cardiac insufficiency can be prevented when treating high blood pressure. As regards a prophylactic effect on coronary artery disease, these investigations do not demonstrate a clear-cut beneficial effect. On the other hand recent data e.g. from Sweden (Berglund et al. 1978) show a reduction of myocardial infarctions by 50 % in a group of middle-aged men with treated hypertension as compared to a reference group. Whether this beneficial effect was due to reduction of elevated blood pressure per se or can be ascribed to the choice of treatment – 80 % of the patients were treated with beta-adrenoceptor blocking agents – cannot be determined at the present time.

There are also solid evidence that antihypertensive treatment has a prophylactic effect on the development of cerebrovascular complications. Several retrospective investigations and in particular the prospective studies of the Veterans Administration Trials demonstrate this fact.

Regarding renal function the effect of antihypertensive treatment is best demonstrated in patients with malignant hypertension. Before the era of effective antihypertensive therapy patients with malignant hypertension could expect only a short period of survival, the cause of death frequently being uremia. Among the trials during the 1950's which demonstrated the positive effect of antihypertensive therapy special reference was made to the trial by Kincaid-Smith et al. (1958). Today malignant hypertension is regarded as being less common than previously. One explanation could be that early treatment of essential hypertension prevents the development of the malignant phase. This view is supported by the results of the Veterans Administration Trials, which demonstrated that antihypertensive treatment prevented the development of renal damage. Also in patients suffering from chronic renal disease, e.g. chronic pyelonephritis with hypertension, investigations by Bengtsson et al. (1968) show an improved prognosis as an effect of antihypertensive therapy.

As regards the cost/benefit question it is difficult to make exact estimates. In one such attempt by Dahlberg (1970) the beneficial effects of the Veterans Administration Studies were applied to the Swedish population. The economic advantage for society was estimated to 200 millions U.S.-dollars annually if antihypertensive therapy was supplied to all patients with diastolic blood pressures above 100 mm mercury. In a study from the National Heart Foundation of Australia in 1970 the estimated reduction in annual mortality from cerebrovascular disease in Australia following the introduction of antihypertensive therapy comprised 2,000 individuals at an annual cost of 25 millions U.S.-dollars (Reader 1974).

From a clinical pharmacological point of view it was stressed that side effects from antihypertensive therapy in part is related to dosage. Increased knowledge, not least as regards the effects of drugs in elderly people, should make it possible to reduce the rate of side effects. A number of factors, besides the level of ar

cause a seeming difference in studies of total amounts of drugs in plasma

Margaretha Groschinsky-Grind

We have examined placental transfer of hydrochlorothiazide and furosemid by taking umbilical blood samples in newborn infants. Hydrochlorothiazide levels are higher but furosemid levels are considerably lower in the child compared to the mother immediately post partum. In addition we find that amnion fluid concentrations of hydrochlorothiazide are about 7 times higher than the plasma levels of mother or child whereas amnion fluid concentrations of furosemid are lower

terial pressure as such influence the results of antihypertensive treatment For this reason it is difficult to give exact cut-off points for blood pressure regarding which patients need antihypertensive treatment or not. In the individual case the physician always has to calculate with a number of conditions such as the general condition of the patient his age his possibilities to adher to the prescribed therapy side effects, and other factors in addition to the level of his blood pressure.

However with all these limitations in mind there was unanimous agreement in the panel that the benefits of antihypertensive therapy far out weigh the negative aspects of such treatment. The cost/benefit aspect is certainly also a very positive one.

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Hemoglobin fortification of food and prevention of iron deficiency with heme iron

By Peter Reizenstein

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Contents

Introduction

Even in 1979 there is much malnutrition in the world A few years ago, anemia was ranked by the WHO Regional office for Africa as one of the five most important medical problems in that region, and here iron deficiency plays a major role

Moreover about 1/4 of the population in Africa and the Far East are undernourished The reasons for this were studied by The World Food Conference in Rome in 1974 It was found that, in addition to distribution problems and economic problems a real food shortage is a major reason. Therefore the utilization of residues like cattle hemoglobin appears logical and useful. This is the motive for the present monograph.

The present results of a comparison of the absorbability of heme iron and vegetable iron suggest that it could be useful to utilize cattle hemoglobin in the prevention of iron deficiency The present results of studies of the nutritional value of meals containing blood proteins suggest that it could also be useful to utilize cattle blood proteins as protein extenders and a source of energy

Chapter I

Prevention of iron deficiency with hemoglobin iron A review of studies of the absorption of heme and non heme iron

Abstract

The relative roles of non-heme and heme iron in preventing iron deficiency are reviewed While it has been difficult to demonstrate in different population groups, any correlation between the intake of non-heme iron and iron deficiency such correlations have been found between the intake of meat and iron deficiency Alternative interpretations of the these findings are discussed

The absorption of non-heme iron under experimental and physiological conditions is reviewed Under experimental conditions and in acute iron deficiency absorption is invariably very good, but under long-term conditions of prophylaxis absorption is reduced and side effects lead to non-compliance of patients This suggests studies of heme iron for prophylactic purposes

Repeated studies between 1945 and 1978 have failed to prove the efficacy of iron fortification, and some suggest that even tablets may not be efficient in the prevention of iron deficiency Concern about possible negative effects of prophylaxis with non-heme iron has increased lately particularly when iron tablets mask the anemia of gastrointestinal cancer Heme iron has only a small advantage in these respects, namely that doses and the maximal absorption are lower

In different studied meals, the heme iron absorption is usually higher than the non-heme iron absorption, probably because the absorption of non-heme iron is inhibited by several constituents of the meal.

The prevalence of iron deficiency is reviewed It is suggested that directed prophylaxis with heme iron in tablet form which can be directed towards at risk groups and away from groups in the gastrointestinal cancer age tablets which can be taken with meals and without side effects should be studied as an alternative to generalized iron fortification

INTRODUCTION

Iron deficiency latent and manifest is still a relatively common problem in some of the industrialized countries and a very common one in developing countries Several attempts to demonstrate the efficacy of non-heme iron to prevent iron deficiency have failed, and concern about possible negative effects of the extensive use of non-heme iron is increasing It has been more difficult to demonstrate a correlation of the frequency of iron deficiency to the intake of non-heme iron than to that of heme iron. These are some of the reasons to discuss the possible use of hemoglobin iron in prevention of iron deficiency

Correlation between the intake of non-heme iron and iron deficiency

If non-heme iron were optimal in preventing iron deficiency a relatively good correlation between the intake of this form of iron and the prevalence of iron deficiency and anemia would be expected It is therefore surprising that no such correlation has been found even when the intake of non-heme iron varied between 6 and 28 mg per day (Davis et al 1967) These negative findings were confirmed by Elwood (1969) in adults and by Samuelsson et al (1972) in children On the other hand a statistically significant ($p < 0\ 01$) correlation ($r=+0\ 44$) could be found by Quist, Ekman and Norden (unpublished) between the total iron intake and the serum ferritin level.

These studies were all done in industrial countries but even more wide variations can be found if developing countries are included For instance Nigeria, India, and Tanzania have average calculated intakes of non-heme iron between 27 and 41 6 mg per capita per day and yet the frequencies of anemia in these countries is considerably higher than in other countries with lower iron-intake (Reizenstein, 1974 Sood et al 1968)

Naturally this is no proof that iron deficiency is independent of the intake of non-heme iron Obviously if the non-heme iron intake becomes extremely low iron deficiency must become a result Also independent differences between the populations and countries compared could obscure the correlation It is obvious that such differences exist regarding health care delivery systems the frequency of diseases like schizostomiasis malaria etc or of alternative dietary deficiencies Nevertheless it is notable that high intakes of non-heme iron may well be associated with a high prevalence of iron deficiency

PREVALENCE OF IRON DEFICIENCY

Manifest iron deficiency is defined as iron deficiency anemia Anemia has often been as a hemoglobin value under the mean value minus 2 standard deviations in a normal population (Vellar et al 1971) For Norwegians in 1970 this would imply that hemoglobin under 14 g/100 ml would be pathologic in men, and under 12 5 g in women However several investigators have used 12 g/100 ml as a border-line (Jungner 1966 Latent iron deficiency anemia is defined as a reduction in the iron content of the body The body stores can be measured only indirectly by estimating the bone marrow iron stores or by measuring the serum ferritin, the unsaturated iron binding capacity the serum ferritin, or the intestinal iron absorption.

Prevalence of manifest iron deficiency anemia

In Sweden a number of studies have indicated that 20 – 25 per cent of women in the fertile age groups had iron deficiency anemia before 1966 (Waldenström, 1946 Garby 1969 Hallberg 1970 Hallberg Hallgren, Holländer Högdahl and Tibblin 1969 Oldfeldt 1968) However one study (Jungner 1966) showed a frequency of only 8 per cent In contrast to the other studies quoted here Jungner s included women older than 50 years After 1966 a rapid decrease in the prevalence seems to have

taken place (Bengtsson et al 1977) In 1963 the mean hemoglobin in fertile women was 122 g/l in 1968 it was 135 and in 1975 it was 136 Iron deficiency is of course much less prevalent among adult men Only about 1 per cent have iron deficiency anemia (Jungner 1966 Tibblin et al 1966) In Denmark, studying 0 5 per cent of a county population, Damberg (1979) found anemia in 8 per cent of women in fertile age groups and in 3 per cent of young men In old men and women, 20 per cent had anemia presumably of different origins In Finland, 2 per cent of young men had less than 130 g and 8 per cent of young women had under 120 g haemoglobin per litre blood; 30 per cent of women lacked stainable iron. Anemia was most common in middle aged women from rural areas Here also anemia was common in the elderly (Takkunen 1976) In Norway (Vellar 1979) 8 per cent of a small sample of men had anemia, which was found mostly in elderly men Of women, 8 8 per cent had anemia in a "poor" and 6 per cent of women in a "wealthy" community In England iron deficiency anemia has been found in between 12 and 25 per cent of women (Kilpatric 1970) and in 2 – 6 per cent of men

In developing countries iron deficiancy anemia may be much more common and found in up to 60 80 per cent of adult women and children (Sood Barney Ramangangswami 1969 Stott 1960 Reizenstein 1974) It has been shown that iron deficiency anemia reduces the physical working capacity if the work load is nearly maximal (Jacobs 1977 a)

Latent iron deficiency

Normal body iron reserves vary between 1 and 2 g A minimum of 0 5 g has been considered to be necessary to meet iron losses during pregnancy etc (Finch 1970) However it is difficult to relate the size of iron stores to the measurable diagnostic findings regarding transferrin saturation, stainable bone marrow iron or intestinal iron absorption. When the reserves are low latent deficiency occurs

It is debatable whether latent iron deficiency causes symptoms In un-controlled studies iron treatment may improve non-specific signs such as tiredness or head aches (Jasinsky 1949 and 1950) but in controlled studies it is difficult to show significant effects (Beutler Larsh and Gurney 1960 Morrow et al, 1968 Elwood Waters Green, Sweetnam and Wood 1969 Elwood et al 1966 Elwood et al 1970) A possible association between iron deficiency and the secretion of nor-adrenalin, or the mono-aminooxidase metabolism has been suggested (Jacobs 1977) It has also been suggested that iron deficiency reduces immunocompetence Fewer infections in children whose iron deficiency had been treated than in the non-treated and defective lymphocyte transformation in iron deficient patients suggested this (Jacobs 1977) So far the only certain signs of latent iron deficiency are decreases of iron containing enzymes such as cytochrome-oxidase (Fairbanks et al 1971 Jacobs 1961 Beutler et al 1960) Ribonuclease may also be iron dependent (Jacobs 1977) and this may explain probably defective proliferation of, e g epithelial cells in iron deficiency

There are very few studies of the prevalence of latent iron deficiency but almost all blood donors have latent deficiency (Högland 1969 Liedén 1973 Magnusson et al 1976) Of women in the fertile age groups, about 40 per cent had increased iron absorption in 1968, and the corresponding figure in adolescent men is 15 per cent (Högland 1969

Höglund et al 1970) In 1975 however only 16 – 18 per cent of women had signs of latent iron deficiency in the form of an increased iron binding capacity without anemia (Bengtsson 1979) and 25 per cent of the women lacked stainable bone marrow iron

ABSORPTION OF NON-HEME IRON

Numerous studies have demonstrated that single doses of iron in the form of ferrous sulfate are well absorbed when given on a fasting stomach particularly by patients with iron deficiency (Bothwell et al 1962 Brise et al 1962 Pritchard et al 1964 Hallberg et al 1967 Callender et al 1969 Heinrich et al 1969 Höglund et al 1969 Reizenstein et al 1973 Norrby 1974 Reizenstein et al 1975) However it is doubtful whether such experimental results are relevant for the prophylaxis of iron deficiency

Under experimental conditions single doses of iron are taken on a fasting stomach, whereas prophylaxis must be performed during prolonged times

Administration at least of appreciable amounts of iron for long times on a fasting stomach has frequently appeared to be difficult There are several reasons for this Firstly prophylaxis is usually given to subjects without symptoms of iron deficiency and for this reason between-meal-medication may be forgotten Even patients with symptoms frequently forget medication (Sackett et al 1975 Malahy 1966 Bengtsson 1972 Gatley 1968 Stewart and Cluff 1972 Malahy 1966 Labolais and Berry 1969 Schwartz et al 1962 Watkins et al 1967 Davies 1968) Secondly if prophylaxis is attempted with large iron doses side effects will interfere with continued medication If prophylaxis of a large population who have little symptoms of iron deficiency to remind them of taking drugs or to make them endure side effects is to be practicable and if prophylaxis is to be continued for many years forms must be devised where treatment can be free of side effects and where tablets can be taken with meals when they are remembered However non-heme iron is frequently given to subjects with the intent of preventing manifest deficiency If the iron is to be given with meals and if the dose is kept low enough to prevent side effects absorption may become unsatisfactory Again there are several reasons for this

One reason is the inhibition of the absorption of non-heme iron by phytates phosphates and other components of the food (Höglund et al 1969 Moore 1969 Elwood et al 1970 Layrisse et al 1971 Rasmussen et al 1972 Martinez-Torres et al 1973 Rasmussen 1975 Reizenstein et al 1975 a) The absorption of from 15 to 20 mg food-iron in latent iron deficiency may reach 20 per cent of the food iron (Finch et al 1950 Crosby et al 1963 Weinfeldt 1965 Norrby et al 1974) at least if the iron forms a part of a meal where it is easily available (Björn-Rasmussen 1979) If the iron deficiency becomes manifest and the meal composition is still favorable to absorption, absorption may be doubled If on the other hand the meal composition is less favorable absorption may be reduced to 5 %

A second reason is the so called marginal tax effect The dose response curve of iron absorption is not linear Much less is absorbed from e g the additional 20 mg added for prophylactic purposes than from the initial 20 mg present in the food

A third possible inhibitor of non-heme iron absorption when iron is administered continuously may be the increased concentration of ionizable iron in the intestinal lumen (Höglund 1969) As a final result, the absorption increase seems to correspond to only 3 % of the additional iron dose or 0 6 mg/day (Liedén 1973 Reizenstein et al 1975 a) when the iron intake is raised from, for instance 20 mg in the food to 40 mg from food and prophylactic non-heme iron This absorption increase is frequently too small to compensate for large menstrual blood losses or for losses from repeated pregnancies or for losses from even slight intestinal hookworm infection (Reizenstein 1974) This may explain why in some developing countries iron deficiency is frequent despite iron intakes as high as 40 mg/day

In many instances, prophylaxis with non-heme iron may be effective nevertheless If patients remember to take tablets between meals if they can tolerate large doses of iron, or if the blood-losses are small this may be the case However there seem to be sufficiently many cases where these conditions are not met to justify the search for alternative prophylactive methods

EFFICACY OF FORTIFICATION WITH NON-HEME IRON IN PREVENTING IRON DEFICIENCY

By far the greatest efforts to prevent iron deficiency have been made with the help of fortification of flour Hundreds of millions of people in England Scandinavia and other countries have been subjected to this form of prophylaxis In comparison prophylactic attempts with iron tablets have been extremely limited

However it has been difficult to demonstrate the efficacy of iron fortification. No effect on the hemoglobin-level could be demonstrated in female mental patients (Elwood 1963) or in healthy women (Elwood et al 1971) Several early studies also failed to show any effect of iron fortification (Mackay et al 1945 Widdowson et al 1954, Harril et al 1957) In Sweden, no decrease in the prevalence of iron deficiency anemia could be demonstrated after the introduction of iron fortification in 1944 The level of fortification was increased in 1963 but studies as late as 1966 showed no decrease in the anemia prevalence A rapid decrease in the prevalence could then be demonstrated between 1966 and 1968 prior to the next increase in the forti fication, 1970 (Bengtsson et al 1977) and prior to an improvement of fortification iron quality (Reizenstein 1977) While it is possible that the frequency decrease about 1967 could be caused in part, by the fortification increase in 1963 no evidence for th cause-effect relationship is available

ALTERNATIVE PREVENTIVE METHODS

It has been proposed that iron fortification can be replaced by oral iron medication, which can be directed to the at-risk-groups (women in fertile age groups, adoles cents blood donors, gastrectomized patients) and away from the groups at risk of iron overload (hemochromatosis porphyria cutanea tarda thalassemia, aplastic anemia, perhaps also stress polycythemia with hypertension and alcoholism) and away from those age groups where gastrointestinal cancer is common

In Sweden, medication with foreseeable life-long duration, such as for instance

folic acid to patients with sprue or vitamin-B_{12} to patients with pernicious anemia is free of charge Iron medication may also be required for many years since it has been demonstrated that menstrual blood losses are relatively constant during the entire fertile period (Hallberg et al 1964) Those women who have high menstrual blood losses will therefore probably require iron supplementation for several decades Therefore it has been proposed that iron supplementation in Sweden to women with high menstrual blood losses and gastroectomized patients be made freely available (Reizenstein 1977) as it is already to blood donors and to pregnant women

However Damberg (1979) has studied the effect of iron tablets containing 20 mg iron on the prevalence of anemia He found no lower hemoglobins in those who did *not* than in those who stated that they did take these tablets He also compared the average sales of iron tablets in 4 countries The range was 1 7 mg/capita per day in England and 6 5 mg i Sweden but apparently he could find no corresponding difference in the prevalence of anemia Damberg (1979) also compared the average intake of fortification iron in mg/person/day (4 7 in Denmark, 8 in Sweden, 1 4 in England) without finding differences in the prevalence of anemia His conclusion is that fortification with non-heme iron is not effective

NEGATIVE EFFECTS OF IRON FORTIFICATION POPULATION GROUPS AT RISK OF SIDE EFFECTS FROM IRON FORTIFICATION

Initially most addition of iron to food aimed at so-called reconstitution of iron levels present in e g flour before sifting Later much higher fortification levels were used but only recently has any sincere discussion of the possible side effects started One has attempted to identify the groups at risk to show side effects and to discuss alternative ways of preventing iron deficiency

Four groups have been discussed In idiopathic hemochromatonis where in some cases the total body iron content is of the order magnitude of 10 grams iron deposition damages the liver pancreas and heart Reduction of the total body iron improves the five year survival from 33 to 89 per cent (Walker et al 1974)

In porphyria cutanea tarda total body iron stores are increased to a lesser degree Here also a reduction of the total body iron decreases symptoms (Lundwall 1971) Iron absorption is increased (Reizenstein, Höglund Landegren, Carlmark and Forsberg 1975 b)

An increased iron intake in patients with hemochromatosis or porphyria tarda causes earlier manifestations of the disease with considerable probality So far however these diseases have been considered so rare that the benefit of iron fortification has been considered to exceed the damaging effects

Lately one has been able to find suspected iron overload in a higher number of cases than previously thought, and several authors emphasize side effects of iron fortification (Crosby 1974 Reizenstein et al 1975 c Olsson 1979) An additional reason to view fortification critically is the fact that iron intakes in iron fortification be-

come highest in the population groups which have the least iron deficiency and possibly the highest risk of side effects namely adult men.
The possible damaging effect of iron fortification is far less certain in cardiac disease although a correlation between high hemoglobin values, high serum lipid values hypertension and cardiac disease has repeatedly been demonstrated (Elwood et al, 1970 Böttiger et al 1972)

An increased iron deposition in the liver of patients with alcoholic cirrhosis has been observed and studies of the possible liver damage resulting from iron deposition in patients with a high iron and high alcohol intake have been, proposed (Reizenstein et al 1975 c) However the only population groups systematically studied in this context are the Bantu in South Africa, with a high consumption of alcohol and iron the form of Bantu-beer The more relevant population groups in countries where iron fortification is currently used seem not to have been studied in these respects

Of all the patients with gastrointestinal cancer 85 per cent have occult blood in the stools and anemia is often the first symptom This anemia can be masked and the diagnosis of gastrointestinal cancer can be delayed by an increased iron intake (Reizenstein et al 1975 c Reizenstein 1977) It has been calculated, that even the increased total absorption of iron resulting from iron fortification may cause relevant delays in the diagnosis in some cases (Reizenstein et al 1975 c) More effective "masking of the anemia may result from prophylactic iron tablets However this masking effect becomes most pronounced if iron medication is erroneously given to anemic patients with gastrointestinal cancer without preceding proper diagnosis Recent studies suggest that such erroneous prescriptions may not be uncommon. The question should be studied if the possible masking of gastrointestinal cancer with iron becomes more common in a country where iron tablet sales are high and actively promoted

It can not be excluded that in the foreseeable future the criticism of iron fortification in its present form will increase Evidence indicates that it is not always an efficient form of preventing iron deficiency and that it may perhaps have damaging effects more often than previously thought. There are therefore good reasons for the drug industry to look for alternative ways of preventing iron deficiency

There is no evidence yet that heme iron could mg for mg cause less potential damage than non-heme iron either in hemochromatosis porphyria cutanea tarda or gastrointestinal tumours although this has been suggested (Reizenstein et al 1975 b Hallberg 1979) However heme iron quantities both when hemoglobin is naturally present in food, or when it is used for fortification or in tablet form, are usually much smaller than non-heme iron quantities In consequence the maximal reported total amount of non-heme iron absorbed in manifest iron deficiency after a single administration is about 40 mg (Norrby 1974) as compared to 3 - 4 mg for heme iron Heme iron, undoubtedly unsuitable for the rapid administration of iron in acute deficiency but possibly suitable for long term prevention, may therefore have fewer potential negative or damaging effects than non-heme iron

Two possible explanations for the difficulty to demonstrate an effect of prophylaxis with non-heme iron must be considered. One is the particular form of non-heme iron used for fortification purposes namely so called reduced, particulate iron. It is probable that variations in the quality of this iron may make it less absorbable

folic acid to patients with sprue or vitamin-B_{12} to patients with pernicious anemia is free of charge Iron medication may also be required for many years since it has been demonstrated that menstrual blood losses are relatively constant during the entire fertile period (Hallberg et al 1964) Those women who have high menstrual blood losses will therefore probably require iron supplementation for several decades Therefore it has been proposed that iron supplementation in Sweden to women with high menstrual blood losses and gastroectomized patients be made freely available (Reizenstein 1977) as it is already to blood donors and to pregnant women

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For this reason the absorption of hemoglobin iron when taken together with a fairly large number of food-stuffs and meals has been studied and compared to that of non-heme iron The meals tested contained both meat and vegetable food Even when hemoglobin iron was compared to ferrous sulphate in a meal consisting only of meat, hemoglobin iron was absorbed better In almost all meals tested heme iron was absorbed between 2 and 3 6 times better than non-heme iron (Chapter II)

It has thus been demonstrated that, while non-heme iron is well absorbed under experimental conditions, it is relatively poorly absorbed under realistic nutritional conditions This may explain why it has been difficult to demonstrate the efficacy even of high level long lasting iron fortification, and why iron deficiency is common even in countries with high intakes of non-heme iron Hemoglobin iron, on the other hand while less well absorbed under experimental conditions than non-heme iron is absorbed between 2 and 3 6 times better in almost all the food combinations and meals tested When taken together with meals hemoglobin iron appears to be preferable

CONCLUSIONS

There are five reasons to study further the possible role of heme iron or hemoglobin iron in the prevention of iron deficiency One is that the efficacy of non-heme iron has been difficult to demonstrate Several studies of the fortification of flour have not shown convincing effects in terms of hemoglobin values

A second reason is that concern exists about possible - largely still hypothetical - negative effects of generalized iron fortification.

A third reason is that wide-spread use of iron tablets containing 37 to 100 mg iron has been shown to mask blood losses from gastrointestinal tumors Hemoglobin tablets containing only 0 4 mg iron are less risky and the possibility that they may be equally effective in preventing iron deficiency should therefore be studied

A fourth reason is that no correlation has been found between the frequency of iron deficiency and the intake of non-heme iron, but that the heme iron intake (meat intake) does seem to show such a correlation

The fifth reason is that hemoglobin iron, when added to some studied meals is absorbed better than non-heme iron. However no large, controlled studies of prevention with heme iron have been published. Such studies are therefore proposed

than iron salts (Högluad and Reizenstein 1969 Rasmussen 1975) However even fortification studies with iron salts have given controversial results (Elwood et al 1971 Stott 1960 Natvig et al 1973 Damberg 1979 Liedén 1973 Reizenstein et al 1975)

CORRELATION BETWEEN THE INTAKE OF HEME IRON AND IRON DEFICIENCY

The difficulties to demonstrate a correlation between the intake of non-heme iron and the prevalence of anemia have been described above However there are some observations which could indicate a possible correlation between the intake of heme iron and the prevalence of anemia

Meat intake and iron deficiency

Heme iron is of course found only in meat fish and food fortified with hemoglobin In countries with a high meat intake such as the USA or Australia, iron deficiency anemia appears to be much less common (Reizenstein 1977) than in countries with low meat intake such as India Differences other than in meat intake between these countries might of course explain the difference in the anemia prevalence but similar observations have been made in a more homogeneous population (Conrad 1970 Takkunen 1976) The decrease in the prevalence of iron deficiency anemia (Bengtsson, Tibblin 1977) noticed during the last decade in Sweden is concomitant with an increase in the meat intake (Reizenstein et al 1979) Again, however no cause-effect relationship can be demonstrated

The most systematic studies of the correlation between meat intake and iron deficiency have been made by Takkunen (1976) who found a statistically significant negative correlation between the unsaturated iron binding capacity in the blood and the meat intake Men with iron deficiency anemia studied in Finland consumed 26 per cent less meat than men with normal blood values (Takkunen 1976) Together these observations suggest, but do no yet prove that an increased meat intake may be associated with a low prevalence of iron deficiency anemia However besides heme iron, meat also contains factors promoting the absorption of non-heme iron (Martinez - Torres et al 1971 Martinez - Torres et al 1973 Layrisse et al 1968) It is also possible of course that the increased heme-iron intake in meat eaters contributes to the prevention of iron deficiency Therefore further studies of the reason for the possible negative correlation between meat intake and iron deficiency are required

COMPARISON BETWEEN THE ABSORPTION OF HEME AND NON-HEME IRON

The absorption of hemoglobin iron under experimental conditions i e, in fasting subjects has been studied repeatedly (Turnbull et al 1962 Hallberg et al 1967 Callender et al 1957 Layrisse et al 1969) and been found to be between 50 and 100 per cent of that of ferrous iron However neither desferrioxamine nor other studied inhibitors of the absorption of ferrous iron can inhibit hemoglobin iron absorption Similarly a normal meal inhibits the absorption of non heme iron (Lindell et al 1963 Conrad et al 1967) but not that of hemoglobin iron (Reizenstein et al 1973 Reizenstein et al 1975 Chapter II)

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Chapter II

Hemoglobin fortification of food
Absorption of hemoglobin and non heme iron

Abstract

A simplified dose response study showed no significant reduction of absorption when the dose was increased from 0.9 to 4.2 mg hemoglobin iron, where absorption was about 20 per cent, but a significant reduction to 11 per cent when dose was increased from 4.2 to 19 mg hemoglobin iron. Nor was any significant absorption inhibition found when 3.5 mg hemoglobin iron were given together with an oatmeal porridge test meal. In contrast, this meal reduced non-heme ferrous iron absorption from 18.7 to 5.5 per cent.

When given on a fasting stomach, no significant difference was found between absorption of hemoglobin and non-heme iron at 3.5 mg dose levels. Numerically, hemoglobin iron was slightly superior.

Meat products, expected to facilitate absorption of non-heme iron were also studied, either given alone or together with a test meal. Mean absorptions of 3.5–10 mg hemoglobin iron in different meals varied between 14.7 and 18.9 per cent, as compared to mean absorptions of non-heme iron between 5.5 and 7.9 per cent.

In contrast, hemoglobin iron absorption was reduced to only 0.8 to 7.6 per cent when baked products, such as bread or liver-paté were studied. Even so, however, mean hemoglobin iron absorptions were 2 to 3 times higher than those of non-heme iron.

The cause of the absorption inhibition in bread was studied. No correlation could be found to the content of bran. No significant inhibition was found when unbaked sour leaven dough was eaten. However, when hemoglobin was heated to baking temperature for baking times, absorption was reduced as in bread. Hemoglobin breakdown during prolonged heating is thus suggested.

No significant difference was found between hemoglobin capsules and hemoglobin tablets.

The present results suggest that hemoglobin fortification can contribute substantial amounts of absorbed iron. A single meal containing about 5 mg hemoglobin iron seems to provide about 0.8 mg of absorbed iron. This alone corresponds to the total iron requirements of a woman with a loss of 30 ml blood per menstruation.

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moglobin with non radio-active hemoglobin produced in an similar way

The hemoglobin was administered in gelatin capsules each containing approximately 400 mg hemoglobin These capsules were taken together with water after an 8 hours fast

SUBJECTS

All absorption studies were performed in subjects suspected to have latent iron deficiency i e women in the fertile age group (Höglund et al 1970) or male blood donors (Lidén 1974) A total of 166 iron absorption tests were performed in 88 such subjects Three different dose levels of hemoglobin iron were studied and hemoglobin was administered in 15 different forms or meal combinations

Dose response

A simple dose response curve for hemoglobin iron absorption was established in 6 blood donors

Heme and non-heme iron absorption

Comparison studies of the absorption of non-heme and heme iron were performed in a total of 64 subjects young females and males where 22 took non-heme iron fasting and in 4 different meal compositions Absorption of hemoglobin iron was studied in 42 subjects who took it fasting and in 6 different meal compositions

Hemoglobin stability during baking

Because it was found that hemoglobin iron is poorly absorbed from bread, different stages of the baking procedure were examined in 2 male blood donors and 1 male volunteer For the same reason, the iron absorption from hemoglobin denatured in three different steps, was studied in 3 volunteer blood donors

Pharmaceutical hemoglobin preparation

In order to study the influence on absorption, the pharmaceutical preparation of hemoglobin absorption was studied in 12 blood donors They were given three different preparations, fasting or together with a test meal, which had previously been found to inhibit the absorption of non-heme iron appreciably and milk (Höglund et al 1970) Two kinds of tablets containing 20 mg hemoglobin iron were kindly prepared by Astra Pharmaceutical Co, Södertälje Sweden, one high and one low pressure tablet. The absorption of hemoglobin iron from the softer and the harder tablet was compared to that of hemoglobin in gelatin capsules

INTRODUCTION

In 1974 the World Health Organization Regional Office for Africa listed anemia as one of the five most important medical problems in that area and iron deficiency is one of the causes of anemia Attempts to prevent iron deficiency anemia have included increasing the iron intake either by fortification or by medicamentation, but almost exclusively with the use of non-heme iron At the present time Sweden seems to have the world's highest level of fortified flour with 6 5 mg iron/100 g flour

However the efficacy of fortification with non-heme iron has been questioned (Reizenstein et al 1979) and it has been difficult to demonstrate any correlation between the intake of non-heme iron and the frequency of iron deficiency anemia (Reizenstein et al 1979)

In contrast iron deficiency seems to be more rare among subjects with a high meat intake and consequently with a high heme iron intake than among subjects getting their iron mostly in the non-heme form (Takkunen 1976) Similarly iron deficiency appears to be more frequent or at least more widely publicized in countries where the iron is derived mainly from cereals or vegetables such as in East Africa parts of Asia and Sweden, than in areas with a high meat and heme iron intake as for instance in the Masai areas of Africa the USA Australia Argentina or Mediterranean Europe Finally it is well kown that the absorption mechanism for heme iron differs from and is less vulnerable than that for non-heme iron *(Reizenstein 1977 Reizenstein et al 1979) Also* cattle hemoglobin is generally a waste product

Therefore the present purpose was to study the absorbability and stability of hemoglobin used for iron fortification

METHODS OF ABSORPTION MEASUREMENTS AND PREPARATIONS

Intestinal iron absorption was studied with a whole body counter as described previously (Reizenstein et al 1961 Reizenstein 1973) The whole body counter employed was designed to compensate for variations in measuring efficiency caused by the redistribution of radio-iron in the human body during the absorption process (Reizenstein 1973) About 0 3-0 5 μCi ^{59}Fe was used for a single absorption study

Preparation of radio-active hemoglobin

Radio-active hemoglobin was prepared by intravenous or intramuscular injection of 1 to 2 5 mCi ^{59}Fe ferric citrate (approximate specific activity 1 mCi per mg) to a calf or a sheep Two to three weeks later the blood from the animals was collected either by sacrificing the animal or by bleeding it The blood was centrifuged and the red cells freeze dried The lyophilized powder consisted of 70 80 per cent hemoglobin The specific activity of the hemoglobin varied between 1 and 5 μCi per g hemoglobin

When necessary this specific activity was reduced by diluting the radio-active he-

In contrast, the absorption decreased statistically significantly ($p<0.05$) to about 11 per cent when hemoglobin iron dose was increased from 4.2 to 19.3 mg (Table 1)

Table 1. Simplified dose-response curve for hemoglobin iron absorption by fasting, male blood donors

Dose of iron, mg	No of subjects	Mean absorption	Se of mean
0.85	6	21.5 %	4.20
4.2	6	20.3 %	4.52
19.3	5	10.8 %	2.41

COMPARISON OF HEME AND NON HEME IRON ABSORPTION

Under experimental conditions, with the iron given on a fasting stomach, the mean absorption of 3.5 mg iron from ferrous sulphate was not statistically significantly different from that of hemoglobin in subjects with latent iron deficiency (Tables 2, 3). However, although the ferrous sulphate was administered in solution, in contrast to the hemoglobin, which was administrered in capsules, the numerical absorption of 3.5 and 4.2 mg hemoglobin iron was slightly higher (18.8 and 20.3 per cent, Tables 1 and 3) than that of 3.5 mg ferrous sulphate iron (16.7 per cent, Table 2)

Table 2. Comparison studies of the absorption of non-heme, ferrous sulphate iron

Type of test	Subjects	Number	Absorption Mean ± S.E.M.
3.5 mg iron, fasting	Young females	8	16.7 ± 4.4
3.5 mg iron, test meal	Young females	6	5.5 ± 2.3
1 mg iron in sausage test meal	Young females	8	7.9 ± 2.3
10 mg iron in dark bread	Apparently healthy male volunteers	8	0.9 ± 0.42
10 mg iron in dark bread with extra bran	Apparently healthy male volunteers	8	0.8 ± 0.25

At a realistic fortification level, between 3.5 and 10 mg iron per meal, and when the iron was administered in the form of a fortified sausage together with a test

Hemoglobin in meat products

The iron absorption from a sausage containing 5 mg non-heme iron and 16 5 mg hemoglobin iron per 100 g was studied It was given together with the test meal described above Each person ate 20 g sausage corresponding to 9 mg non heme iron and 3 5 mg heme iron Hamburgers and baked liver-paté were prepared containing 10 mg hemoglobin per portion

Hemoglobin in bread

Three different kinds of bread were fortified with ferrous iron or hemoglobin White sifted wheat flour bread brown whole meal rye bread and brown whole meal bread with extra bran added were used Two hemoglobin fortification levels were used one with 1 mg iron per portion the other with 10 mg iron

Unbaked wheat and whole meal dough used for white and brown bread respectively was given to 3 volunteers The amount of heme iron per portion was the same as that given in the finished bread Since the hemoglobin used to fortify bread is subjected to a pH about 4 at 90 C for 60 minutes during the baking hemoglobin similarly treated was fed to the same 3 volunteers in order to study the absorption of iron from denatured hemoglobin

The denaturation of hemoglobin was performed by heating to 110 C for 1 minute at pH 7

Bleached hemoglobin - a protein extender

A bleached hemoglobin product is being produced in Sweden, to be used as a protein extender To study the iron absorption from this product bleached in the laboratories of Ellco Protein with H_2O_2 and HCl amounts containing 3 5 mg iron were given to test persons as well as meat ball portions containing 3 5 mg iron derived from bleached hemoglobin

The preparation of the 15 different foods or food components fortified with ferrous iron or native or bleached hemoglobin was performed by Mrs Birgit Slesby Department of Meat Technology Royal Agricultural School Copenhagen Denmark, by Mr Agne Bergkvist Swedish Meat Research Institute Kävlinge Sweden by Mr I Forslund Schulstad Bakery Copenhagen Denmark, by Kungsörnen Bakery Södertälje, Sweden and by Globe Foods Stockholm Sweden Their co-operation is gratefully acknowledged

RESULTS

Response of absorption to hemoglobin dose

No statistically significant decrease in absorption was found when the hemoglobin dose was increased from 0 85 to 4 2 mg hemoglobin iron per meal (Table 1); the absorption remained about 20 per cent

In contrast, the absorption decreased statistically significantly ($p < 0 05$) to about 11 per cent when hemoglobin iron dose was increased from 4 2 to 19 3 mg (Table 1)

Table 1 Simplified dose-response curve for hemoglobin iron absorption by fasting, male blood donors

Dose of iron, mg	No of subjects	Mean absorption	Se of mean
0 85	6	21 5 %	4 20
4 2	5	20 3 %	4 52
19 3	5	10 8 %	2 41

COMPARISON OF HEME AND NON-HEME IRON ABSORPTION

Under experimental conditions with the iron given on a fasting stomach, the mean absorption of 3 5 mg iron from ferrous sulphate was not statistically significantly different from that of hemoglobin in subjects with latent iron deficiency (Tables 2 3) However although the ferrous sulphate was administered in solution, in contrast to the hemoglobin, which was administrered in capsules the numerical absorption of 3 5 and 4 2 mg hemoglobin iron was slightly higher (18 8 and 20 3 per cent, Tables 1 and 3) than that of 3 5 mg ferrous sulphate iron (16 7 per cent, Table 2)

Table 2 Comparison studies of the absorption of non-heme, ferrous sulphate iron.

Type of test	Subjects	Number	Absorption Mean ± S.E.M.
3 5 mg iron - fasting	Young females	8	16 7 ± 4 4
3 5 mg iron test meal	Young females	6	5 5 ± 2 3
1 mg iron in sausage test meal	Young females	8	7 9 ± 2 2
10 mg iron in dark bread	Apparently healthy male volunteers	8	0 8 ± 0 42
10 mg iron in dark bread with extra bran	Apparently healthy male volunteers	8	0 8 ± 0 25

At a realistic fortification level between 3 5 and 10 mg iron per meal and when the iron was administered in the form of a fortified sausage together with a test

meal the absorption of hemoglobin iron (17 8 per cent, Table 3) was twice as high as that of ferrous sulphate (7 9 cent Table 2) This difference was statistically significant ($p < 0\ 001$) In spite of the expected absorption promotion of non-heme iron by the meat in the sausage In fact the hemoglobin iron absorption percentages from up to 10 mg iron in all non-baked foods or food components (Tables 3 and 4) seem to supply 1 5 - 1 8 mg absorbed iron per fortified portion

Hemoglobin iron absorption from bread

The absorption was 4 to 10 times lower from bread (1 5 to 3 8 per cent) than from sausage or hamburger (Table 3) The absorption inhibition seemed unrelated to the bread content of iron absorption inhibitors known to be present in bran (Table 3) Thus absorption was as low from white bread as from whole meal bread (Table 3) Similarly when the phytic acid content of bread was artificially increased by the addition of bran, no significant inhibition of hemoglobin iron absorption could be found (Table 3)

Table 3 Absorption of hemoglobin iron

Meal composition	Subjects	No of subjects	Absorption Mean ± S.E.M
3 5 mg hemoglobin iron in capsules-fasting	Young male blood donors	14	18 8 ± 3 3
3 5 mg hemoglobin iron in sausage + test meal	Young female and male blood donors	14	17 8 ± 1 45
10 mg hemoglobin iron in hamburger	Young male and female blood donors	8	14 7 ± 6 11
10 mg hemoglobin iron in baked liver-paté	Young male and female blood donors	8	7 6 ± 5 34
1 mg hemoglobin iron in baked white bread	Young male and female blood donors	6	1 5 ± 0 72
10 mg hemoglobin iron in baked brown bread	Apparently healthy male volunteers and blood donors	8	3 8 ± 1 59
1 mg hemoglobin iron in baked brown bread	-'-	6	1 6 ± 1 28
10 mg hemoglobin iron in brown bread baked with extra bran	-"-	8	2 8 ± 0 53

At the 10 mg iron level the absorption of hemoglobin from brown bread was lower (2 8-3 8%, Table 3) than that from meat, but the absorption of ferrous iron was even worse (0 8-0 9% Table 2)

Less iron was absorbed from dark bread at the 10 mg level from ferrous iron (ab 0 8 per cent) than from hemoglobin used for the fortification of bread (2 8 to 3 8 per cent Tables 2 and 3) but this difference was not significant statistically

Table 4 Iron absorption from 1 mg iron in hemoglobin at different stages of the baking process, and from bleached hemoglobin

Form and conditions of administration	Material	No of subjects	Absorption, mean % ± S E of mean
Baking			
Wheat dough (pH 6) fasting subjects	Hemoglobin in dough	2 blood donors + 1 male volunteer	18 9 ± 14 61
Dark sour dough (pH 4) prior to baking fasting subjects	Hemoglobin in dough	2 blood donors + 1 male volunteer	12 6 ± 9 58
Hemoglobin, heated to 90 C at pH 4 for 60 minutes fasting subjects	Heated hemoglobin	2 blood donors + 1 male volunteer	4 5 ± 0 75
Bleached hemoglobin			
Capsulated; fasting subjects	Denatured bleached hemoglobin	3 blood donors	5 4 ± 0 85
Capsulated, with test meal	Denatured bleached hemoglobin	3 blood donors	0 3 ± 0 57
In fortified meat balls	Denatured bleached hemoglobin	3 blood donors	1 7 ± 3 0
Comparison			
Capsulated; fasting subjects	Native hemoglobin	2 blood donors + 1 male volunteer	14 1 ± 3 93

meal the absorption of hemoglobin iron (17 8 per cent Table 3) was twice as high as that of ferrous sulphate (7 9 cent Table 2) This difference was statistically significant ($p < 0\ 001$) in spite of the expected absorption promotion of non heme iron by the meat in the sausage In fact the hemoglobin iron absorption percentages from up to 10 mg iron in all non-baked foods or food components (Tables 3 and 4) seem to supply 1 5 - 1 8 mg absorbed iron per fortified portion

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1 mg hemoglobin iron in baked white bread	Young male and female blood donors	6	1 5 ± 0 72
10 mg hemoglobin iron in baked brown bread	Apparently healthy male volunteers and blood donors	8	3 8 ± 1 59
1 mg hemoglobin iron in baked brown bread	- -	6	1 6 ± 1 28
10 mg hemoglobin iron in brown bread baked with extra bran	- -	8	2 8 ± 0 63

At the 10 mg iron level the absorption of hemoglobin from brown bread was lower (2 8-3 8% Table 3) than that from meat but the absorption of ferrous iron was even worse (0 8-0 9% Table 2)

Table 5 Effect, on hemoglobin iron absorption, of the pressure used when preparing hemoglobin tablets, or encapsulation of hemoglobin.
(Fasting blood donors given 20 mg hemoglobin iron.)

Form of preparation	No of subjects	Absorption Mean ± S E of mean, in per cent
Low pressure tablet	6	10 0 ± 2 78
High pressure tablet	5	8 3 ± 2 63
Gelatin capsule	8	9 0 ± 2 12

If hemoglobin fortification would result in an approximate intake of 3 5 mg hemoglobin iron per main meal or 7 mg of hemoglobin iron per day an average iron absorption *of approximately 1 mg per day would be achieved from this alone* This is appreciably more than the calculated absorption from the iron presently used for the fortification of flour (Höglund et al 1970 Heinzenstein et al 1979)

Prevention of iron deficiency can take the form of food fortification or of food supplements Hemoglobin iron appears to be suitable mainly for the prevention, not for the treatment of iron deficiency since its iron content is low Hemoglobin administration will result in iron intakes at a therapeutic level only if exceptional methods are used such as giving large amounts of hemoglobin granulates on food It is true that isolated heme has a higher iron content than hemoglobin, but unless the heme molecule is changed, absorption will be unsatisfactory

However even if special methods could be used to administer larger amounts of hemoglobin or heme iron, the present studies show that one would rapidly approach a point of diminishing returns There is a sharp drop in the absorption at absorption levels somewhere between 4 3 and 10 3 mg

Since cereals generally contain iron absorption inhibitors, it was hoped that hemoglobin iron fortification of cereal products could replace to some extent, the conventional fortification with non-heme, metallic so-called reduced iron. However the present results suggest a hemoglobin breakdown during the prolonged heating when bread is baked The low pH *in sour dough* seems less harmful This breakdown may also explain the relatively low absorption of hemoglobin iron used for the fortification of liver-paté which is also baked, although at lower temperatures and for shorter times (80 C 45 minutes)

In spite of the heme break-down, the absorption of the remaining intact hemoglobin iron from bread results in significantly higher uptake than ferrous sulphate fortification There are reasons to assume that *heme iron absorption* is even more superior to that of the conventionally used metallic iron (Höglund et al 1970 Björn Rasmusson et al 1977)

Hemoglobin stability during baking

Since the low absorption in bread seemed unrelated to the bran content, the effect of temperature and pH during baking was examined The absorption was statistically significantly inhibited neither in unbaked cold wheat dough nor in unbaked sour dough (Table 4) In contrast when hemoglobin was heated to 90 C at pH 4 for 60 min a pH and temperature corresponding to those used during baking a statistically significant (< 0 05) decrease in the mean absorptions was found (Table 4)

Hemoglobin iron absorption from meat products

Statistically significantly (p<0 05) more iron was absorbed from hemoglobin used to fortify (non-baked) hamburgers or meat sausage than from that used to fortify baked liver-paté (Table 3) Heat denaturation during baking of the paté is believed to explain this difference The absorption from 10 mg hemoglobin iron in hamburgers was not statistically significantly lower than that of 3 5 mg hemoglobin iron given on a fasting stomach (Table 3)

Iron absorption from bleached hemoglobin

Hemoglobin is bleached by the food industry in order to obtain a protein powder without the heme colour to be used as a replacement protein Even when this powder was given on a fasting stomach and despite the use of a dose of only 1 mg iron, the percentage absorption was statistically significantly lower from the protein powder than from native hemoglobin (Table 4) Moreover when this denatured hemoglobin powder was given together with a test meal a statistically significant (p < 0 01) inhibition of the iron absorption was found This was true for two different test meals (Table 4) and suggests that the iron in the bleached hemoglobin is partially or largely non-heme iron

EFFECT OF THE PHARMACEUTICAL HEMOGLOBIN PREPARATION

No statistically significant difference could be found between the absorption of labelled hemoglobin iron given in the form of a capsulated powder a soft low-pressure tablet and a hard high pressure tablet (Table 5)

CONCLUSIONS

The use of hemoglobin iron for the fortification of meat products seems to result in satisfactory iron absorption No evidence was found in the present study of any inhibition of the iron absorption by cereals eaten together with the hemoglobin iron It is reasonable to assume that even if non-heme iron was used for the fortification of meat products which enhance its absorption rather than for that of bread which inhibits it, it would still be much less well absorbed than hemoglobin iron (Tables 2 and 3) This seems to be true even when ferrous sulphate is used as the non-heme iron The reduced metallic iron normally used for fortification purpose in Sweden is usually even less well absorbed than ferrous sulfate (Höglund et al 1970)

Table 6 Effect, on hemoglobin iron absorption, of the pressure used when preparing hemoglobin tablets, or encapsulation of hemoglobin.
(Fasting blood donors given ~0 mg hemoglobin iron.)

Form of preparation	No of subjects	Absorption, Mean ± S E of mean, in per cent
Low pressure tablet	6	10 0 ± 2 78
High pressure tablet	6	8 3 ± 2 63
Gelatin capsule	8	9 0 ± 2.12

If hemoglobin fortification would result in an approximate intake of 3 .5 mg hemoglobin iron per main meal, or 7 mg of hemoglobin iron per day an average iron absorption of approximately 1 mg per day would be achieved from this alone This is appreciably more than the calculated absorption from the iron presently used for the fortification of flour (Höglund et al 1970 Reizenstein et al 1979)

Prevention of iron deficiency can take the form of food fortification or of food supplements Hemoglobin iron appears to be suitable mainly for the prevention, not for the treatment of iron deficiency since its iron content is low Hemoglobin administration will result in iron intakes at a therapeutic level only if exceptional methods are used, such as giving large amounts of hemoglobin granulates on food. It is true that isolated heme has a higher iron content than hemoglobin, but unless the heme molecule is changed, absorption will be unsatisfactory

However even if special methods could be used to administer larger amounts of hemoglobin or heme iron, the present studies show that one would rapidly approach a point of diminishing returns There is a sharp drop in the absorption at absorption levels somewhere between 4 3 and 19 3 mg

Since cereals generally contain iron absorption inhibitors, it was hoped that hemoglobin iron fortification of cereal products could replace to some extent, the conventional fortification with non-heme, metallic, so-called reduced iron. However the present results suggest a hemoglobin breakdown during the prolonged heating when bread is baked The low pH in sour dough seems less harmful This break-down may also explain the relatively low absorption of hemoglobin iron used for the fortification of liver-paté which is also baked although at lower temperatures and for shorter times (60 C 45 minutes)

In spite of the heme break-down, the absorption of the remaining intact hemoglobin iron from bread results in significantly higher uptake than ferrous sulphate fortification. There are reasons to assume that heme iron absorption is even more superior to that of the conventionally used metallic iron (Höglund et al 1970 Björn-Rasmussen et al 1977)

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Chapter III

Intestinal absorption of heme iron in man

Abstract

There are 4 reasons to examine heme iron absorption
1 Vegetabilic diets and iron deficiency anemia in developing countries
2 difficulties to refill iron stores in women in industrialized countries
3 non-use of cattle hemoglobin for human nutrition and
4 differences in absorption between heme and non-heme iron. Twenty-eight different preparations and combinations of ^{59} Fe-heme were fed to 84 volunteers with latent iron deficiency

Four methods to prepare heme were tested UV-spectrophotometry used to examine the degree of heme polymerization showed unprecise spectra for heme prepared with acetic acid acetone which suggests polymerization About 40 mg histidine/mg heme sharpened spectra probably since dihistidine-heme monomers were formed

Calculations described earlier indicate that the net absorption increase when the diet is supplemented with 20 mg ferrous iron daily and when the iron is given with meals is only 0 8 mg/day In contrast, it has been calculated that if 20 mg hemoglobin iron are given it is 2 2 mg/day If 20 mg heme iron in ordinary or enteric-coated capsules was given alone or together with buffering substances absorption was unsatisfactory (about 0 15 mg iron)

It was also unsatisfactory (about 0 4 mg) from solutions containing glycine or histidine However satisfactory absorptions (about 2 mg) were obtained from a buffered pH 6 water solution of hemin containing nicotinic acid and of an oil solution of hemin-di-methyl ester

INTRODUCTION

Iron deficiency anemia is a common disease in developing countries for a number of reasons outlined earlier (for references see Reizenstein 1974) Iron intake in several developing countries is appreciably higher than it is in industrialised countri a, but in many areas consists of almost exclusively non-heme iron, the intestinal absorption of which is inhibited by largely vegetabilic diets

In industrialised countries, iron deficiency anemia is becoming relatively rare However latent iron deficiency (i e depleted iron stores) is still common (for references see Hallberg et al 1970 Kief 1975) The reason appears to be that absorption of the largely non-heme therapeutic or supplemental iron is strongly stimulated as long as there is anemia, but that absorption decreases sharply when the hemoglobin concentration approaches normal The stimulation during the

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4 Acetic acid extraction (Labbe et al 1957 Falk 1967) was found to be the most suitable method

Characterization of porphyrin

Attempts were made to examine with u.v spectrophotometry the aggregation and polymerization condition of the porphyrins isolated

Hemin iron preparations

Customary procedures were used when solubilizing compounds (NaOH Na_2CO_3 and the basic amino-acid arginine) and co-ordinating compounds like nicotinic acid (tab 1) nicotinamide xylitol pentanicotinate and histidine were added (tab 1) Buffers sometimes containing ascorbic acid or glycine were used in some experiments (tab 1) An attempt was made to prevent polymerization of hemin molecules, previously attributed to bridges between propionic acid side chains on the porphyrin ring by derivatisation of this group to methyl ester (Falk 1967) Enteric coating of some preparations was performed by customary methods

Iron absorption measurements were performed as previously described with a whole body counter (Reizenstein et al 1961)

RESULTS

Absorption of hemoglobin iron

Five subjects with latent iron deficiency absorbed an average of 2 2 mg of 20 mg hemoglobin iron given in capsules with or without food Administration prolonged for 7 days did not appear to reduce absorption Comparison values for non-heme iron (0 8 mg) are given in the discussion below

Characterization of porphyrin

Hemin (Fe^{+++}) dissolved in a $NaHCO_3/Na_2CO_3$ buffer at pH 11 was found to give ill-defined uv-spectrophotometric peaks in the maxima 380–390 465–500 520–540 (shoulder) and 610–620 μ region even after acidification or the addition of pyridine as a co-ordinating ligand On the other hand heme (Fe^{++}) obtained by reducing hemin solutions with sodium dithionite gave 4 sharp absorption bands in the u.v spectrum at 416 480 524 540 (min.) and 558 μ, after the adding of pyridine When histidine was added to a $10^{-2}-10^{-4}$ M heme solution, this resulted in a sharper spectrum than that found in heme alone None of the other amino acids tested had a similar effect

Absorption of hemin from ordinary capsules

When hemin was encapsulated alone or together with sodium bicarbonate only an

anemic phase seems to overcome the inhibition of iron absorption effected by food and a prolonged high iron concentration in the intestine During the phase of latent iron deficiency these effects dominate and they together with the so-called 'marginal tax effect (Reizenstein et al 1975 d) caused by the shape of the dose-response curve explain why the net increase in iron retention during iron therapy is so small that stores become repleted exceedingly slowly

Hemoglobin iron is absorbed no better than non-heme iron under experimental conditions i e in single doses on a fasting stomach However its absorption seems to be less inhibited by food and heme does not increase the concentration of ionic iron in the intestine During realistic nutritional or therapeutic conditions it might therefore have some advantages (Reizenstein et al 1975 c och d) There are in fact some observations indicating that meat-eating populations have less iron deficiency than those eating vegetabilic diets (Reimann et al 1970 Takkunen 1976)

Only about 10 % of the hemoglobin produced by Swedish slaughterhouses is used for human consumption (Reizenstein 1975 a och b) In countries with productions much higher than Sweden the percentage is probably smaller

Thus large quantities of heme iron as well as of globin are available as sources of possible valuable dietary supplemental or therapeutic iron

These are the four main reasons for the present study of the solubility and absorbability of heme and of its state of aggregation

Materials

Radio-active hemoglobin was prepared by injecting 750 $\mu Ci\, ^{59}FeCl_3$ intravenously to calves being sacrificed 2 weeks later From their carotid arteries approximately 4 l blood was obtained and collected in sterile 1 litre bottles containing 80 ml 0 2 % sodium citrate Bottles were flown or transported to an Ecal Food Drier (E Carlsson Munka Ljungby) and blood was dried at 70 C Radio-iron absorption was studied in 84 volunteer blood donors with latent iron deficiency

METHODS OF SEPARATING HEME AND GLOBIN OF CHARACTERIZING PORPHYRINS AND OF PREPARING HEME IRON

Separation of heme hemin or hematin from globin

The following methods were tested

1 Trypsin digestion (Conrad et al 1967 a och b) with and without pre-denaturation (100 C 10 min) was not used because only 33 per cent of protein was recovered in lyophilized dialysates
2 Glacial acetic acid (Fischer 1941) precipitation followed by dialysis against 0 9 per cent NaCl was not used since it resulted in unsatisfactory recovery of crude hemin precipitates
3 Methyl-ethyl-ketone extraction (Yonetani 1967 Teale 1959) was not used despite 75 per cent protein recoveries because of high solvent requirements

It appears probable both when considering hemoglobin iron absorption and in regard to the present results that monomeric non-aggregated soluble heme would be absorbable The problem is that the solubility qualities of heme are complicated and that it forms polymers and aggregates easily

Heme has two carboxylic acid or propionamide and two vinyl side chains It is partly lipid soluble and partly water soluble The reason for this is probably the arrangement with the lipophilic vinyl side chains of heme fixed in a hydrophobic pocket (Antonini 1971) in the globin molecule while the hydrophilic propionamide side chains are sticking out into the mainly aqueous biological environment

Esterification of the carboxylic acid side chains increases the solubility in organic solvents (Falk 1967) If the polar side chains could be removed like in aetioporphyrin which has only vinyl side chains, solubility in lipid solvents would increase (Falk 1967) Similarly if all vinyl side chains could be removed or replaced heme would become entirely water soluble These facts explain why heme is poorly soluble and absorbable although it resembles compounds such as vitamin B_{12} uro porphyrin I and coproporphyrin I and II, which are more easily soluble

These considerations also explain why better absorption was obtained when heme was solubilized either in oil by esterification of the polar side chains or in water by alcalization with sodium carbonate or sodium hydroxide However solubilization of heme is not enough to obtain optimal absorption; polymerization and dimerization must also be prevented (Antonini 1971) Polymerization may take place via OH - links between the iron atoms Both heme and hemin in water are at least dimeric (Ehrenberg 1957) and the free iron co-ordination sites are occupied by water or hydroxyl ions, depending on pH

Polymerization is difficult to avoid since experiments usually have to be performed in alkaline solutions (Falk 1967) Polymerization is less pronounced in ferri-coproporphyrin, which has 4 propionic acid polar side chains and thus a large electrostatic field, or ethanol (Falk 1967) Since it is thought that sharp bands indicate the formation, by pyridine of the monomeric bispyridyl complex from the original dimeric bisaquo-heme complex or (in neutral solution) from large ionic micellae (Ehrenberg 1957 Kellin 1965) u v spectrophotometry was used to characterize porphyrins in the preparations tested

Histidine forms one of the ligands between the globin molecule and the iron in hemoglobin (Antonini 1971); these ligands seem to have a special function compared to the 10 other amino acids within van d r Waals constant distance of the porphyrin (Antonini 1971)

For this probable reason the addition of histidine was found, at high concentrations to sharpen the heme spectrum by preventing *dimerization* This effect however could not be used in practice for two reasons First, a large amount of histidine was found to be required per molecule of heme (approximately 40 mg/g heme) This is in agreement with Ehrenbergs (1957) *finding* that 0 14 M histidine solutions are required to form heme-di-histidine Secondly single amino acids at neutral pH are zwitterions and poly-amino-acids would probably offer a better chance to prevent polymerization (Lemberg 1961 Bauer et al 1963)

average of 0 14 mg was absorbed (experiments 1 3 13 and 22 in Table I) from 20 mg hemin iron

Absorption of hemin in enteric coated capsules

Of 20 mg hemin iron encapsulated alone or together with histidine arginine sodium carbonate nicotinic acid only an average of 0 16 mg was absorbed (experiments 2 4 7 8 14 23 in tab 1)

Absorption of hemin in solutions

The absorption was poor (0 4 mg of 20 mg heme iron) when a solution of hemin in *glycine and NaOH was given When histidine xylitol pentanicotinate* or ascorbic acid were added no appreciable improvement was noted (experiments 5 6 9 10 15 16 17 18 19 20a 20b 27)

The absorption was satisfactory of 20 mg heme iron dissolved at pH 8 0 with addition of histidine (2 mg/mg heme) sodium carbonate (1 65 mg/mg) nicotinic acid (0 8 mg/mg) and ascorbic acid (2 mg/mg) An average of 3 mg was absorbed (experiment 10) The absorption was also satisfactory of hemin methyl di-ester dissolved in arachid oil An average of 2 mg was absorbed (experiments 20 B and 26)

However the absorption from the water solution sank to 1 4 mg when nicotinic acid was exchanged for nicotinamide and to 0 84 mg when arginine replaced sodium carbonate and nicotinic acid It also sank, to 0 46 mg when the doses were reduced of histidine (to 0 4 mg/mg) nicotinic acid (to 0 18 mg/mg) and of ascorbic acid (to 0 4 mg/mg in experiments 5 6 9 10) The absorption from the oil sank to about *0 4 mg when the ester was suspended in oil rather than dissolved* or when it was given in capsules

DISCUSSION

Comparison values for the absorption of non-hemin iron

Earlier studies (Reizenstein et al 1975a and b) showed that subjects with latent iron deficiency absorbed on an average 4 mg iron *of a single 20 mg iron dose* in the form of $FeSO_4$ given on a fasting stomach and 2 2 mg when the iron was given with food When continuous daily doses were given on a fasting stomach 2 8 mg were absorbed from each dose

Assuming a daily food iron intake of 20 mg the daily addition of 20 mg iron as $FeSo_4$ taken with food was calculated to increase the total absorption of iron by only 0 8 mg/day

Since 2 2 mg were absorbed from 20 mg hemoglobin iron, and since this seems not to be inhibited by food it could be assumed that persons with a 20 mg food iron intake would increase their net absorption by 2 2 mg per day if 20 mg hemoglobin iron was added daily or 2-3 times the amount found for non-hemin iron.

Tabl I Int tinal absorption, by apparently healthy blood donors, of iron afte administration of 20 mg hem iron in 29 diff rent forms or compositions

Experiment No	Iron preparations	Rationale	No of Subjects	% Absorbed
1	Hemin 250 mg in ordinary capsules	Therapeutic dose given as ordinary capsule to test absorption of hemin iron in the absence of amino acids	7	< 1
2	Hemin 250 mg in enteric coated capsules	Therapeutic dose given as an enteric coated capsule with capsule disintegration to start at pH 5–6 This study was meant to avoid exposing the hemin to the acid conditions of the stomach	7	< 1
3	Hemin 45 mg in ordinary capsules	Tracer dose to assess whether dose size of hemin influenced the absorption of hemin iron	8	< 1
4	Hemin 45 mg in enteric coated capsules	As study 3 but given as enteric coated capsules	8	3 7
5	20 ml solution pH 8 containing Hemin 250 mg Arginine 500 mg Histidine 500 mg Ascorbic Acid 450 mg	Hemin dissolved in a solution containing histidine which was reported as successful in improving the absorption of iron from hemoglobin Arginine was the only basic amino acid in solution that would dissolve hemin Ascorbic acid was incorporated to maintain the pH at 8	4	4 2 $\pm$ 1 6

In conclusion heme iron is well absorbed from hemoglobin where the globin keeps heme soluble and prevents polymerization When globin is split off heme solubility becomes a problem and at the pH where it is soluble hydroxide bridges between iron cause at least dimerization and probably polymerization

Heme is soluble in alkali but this solubility could problably be increased if the vinyl side chains could be replaced It can also be made soluble in oil if the polar carboxylic acid side chains are esterified but some polymerization of the ester seems to occur

Polymerization can be prevented by forming heme – dihistidine but this requires unpractically large quantities of histidine It appears probable that absorbable monomeric soluble heme will be obtained only when the free ligands of iron have been blocked and when simultaneously heme has either been made water soluble by modification of the vinyl side chains or lipid soluble by the modification of the polar side chains

Experiment No	Iron preparations	Rationale	No of Subjects	% Absorbed
10	20 ml solution pH 8 containing Hemin 250 mg Histidine 500 mg Nicotinamide 200 mg Ascorbic Acid 500 mg Sodium Carbonate 400 mg	Nicotinamide was substituted for nicotinic acid as the latter resulted in considerable subject discomfort due to its vasodilatory properties	4	7 2 ± 1 3
13	Hemin 250 mg Nicotinic Acid 200 mg Sodium Carbonate 150 mg Histidine 100 mg Ascorbic Acid 100 mg In ordinary capsules	Preparation 9 given in ordinary capsule form	4	3 1 ± 2 1
14	Hemin 250 mg Nicotinic Acid 200 mg Sodium Carbonate 150 mg Histidine 100 mg Ascorbic Acid 100 mg In enteric coated capsules	Preparation 9 given in enteric coated capsule form to protect from the stomach acid content	4	0
15	Hemin 250 mg Glycine 680 mg Sodium Hydroxide 40 mg *In 10 ml of water pH 8*	The amino acids in the above preparations may not have sufficient buffering capacity to overcome the stomach acids Hemin was therefore dissolved in a high capacity glycine buffer for absorption studies	4	2 0 ± 1 4

Experiment No	Iron preparations	Rationale	No of Subjects	% Absorbed
6	20 ml solution pH 8 containing Hemin 250 mg Sodium carbonate 400 mg Histidine 500 mg Nicotinic Acid 200 mg Ascorbic Acid 500 mg	Hemin in solution containing histidine and ascorbic acid for the reasons stated above Sodium carbonate inorganic base to promote solubilisation of hemin Nicotinic acid reported to promote absorption of small quantities of hemin when given in large excess	4	14 9 $\pm$ 2 9
7	Hemin 250 mg Histidine 250 mg Arginine 250 mg In enteric coated capsules	Preparation similar to 5 but presented as an enteric coated capsule to protect the ingredients against the acid contents of the stomach On disintegration of the capsule at pH 5 6 the arginine should assist in solubilising hemin	4	0 2 $\pm$ 0 3
8	Hemin 250 mg Histidine 250 mg Sodium Carbonate 250 mg In enteric coated capsules	As 7 but with sodium carbonate added as the base	3	1 0 $\pm$ 0 5
9	Hemin 250 mg Sodium Carbonate 100 mg Histidine 100 mg Nicotinic Acid 45 mg Ascorbic Acid 100 mg In 20 ml solution pH 8	The same ingredients as 6 Reduced amounts of amino acids to see wether the high absorption recorded for 6 was dependent upon the molar concentration of the amino acid	4	2 3 $\pm$ 0 3

Experiment No	Iron preparations	Rationale	No of Subjects	% Absorbed
19	Hemin Methyl ester (250 mg) in ordinary capsules	Esterification of hemin gave the diester which was shown on Sephadex to have a molecular weight of 700 indicating it existed as a monomer in organic solvents	4	0 2 ± 0 1
20 A 20 B	Hemin methyl ester (250 mg) in vegetable oil (7 ml)	Diester mixed with vegetable oil in which it was partially soluble could result in improved iron absorption	4 2	0 2 ± 0 11 (for diester suspended in oil) 5 7 - 12 3 (diester soluble in oil)
21	Hemin sodium salt 50 mg Sodium bicarbonate 50 mg taken with water 50 ml	Hemin sodium salt readily soluble in water (pH 7) This sodium salt could result in improved absorption compared to hemin	4	6 5 ± 0 5
22	Hemin sodium salt 250 mg Sodium bicarbonate 50 mg in ordinary capsules	The sodium salt tested in capsule form	3	3 6 ± 1 9
23	Hemin sodium salt 250 mg Sodium bicarbonate 50 mg	Sodium salt tested in enteric coated capsule form	4	3 0 ± 3 0

Experiment No	Iron preparations	Rationale	No of Subjects	% Absorbed
16	Hemin 250 mg Glycine 680 mg Sodium Hydroxide 40 mg Histidine 100 mg in 10 ml of water pH 8	As 15 Administered with histidine Spectrometric studies shows a significant sharpening of the hemin spectrum in glycine buffer containing histidine This sharpening was attributed to monomerisation of hemin in solution	3	3 1 ± 1 6
17	Hemin 250 mg Glycine 680 mg Sodium Hydroxide 40 mg Xylitol penta-nicotinate 400 mg in 10 ml of water pH 8	As 15 Administered with xylitol pentanicotinate as a source of nicotinic acid	4	2 2 ±1 3
18	Hemin 250 mg Glycine 680 mg Sodium Hydroxide 40 mg Ascorbic Acid 400 mg in 10 ml of water pH 8	As 15 Administered with ascorbic acid	3	1 1 ± 0 3

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Experiment No	Iron preparations		Rationale	No of Subjects	% Absorbed
24	Hemin Sodium hydroxide	250 mg 40 mg	This experiment was carried out to study alkaline solution of heme	9	6 5 $\pm$ 3 9
25	Hemin Milk of Magnesia	250 mg 10 ml	Milk of Magnesia has a pH 10 and it was felt that hemin given in this basic media could improve absorption	4	3 3 $\pm$ 1 4
26	Hemin Sodium hydroxide Ascorbic acid taken in water	250 mg 40 mg 400 mg 20 ml	As study 24	1	8 7
27	Hemin ester Alcohol 68 Propylene glycol Sorbitol syrup Glycerin	250 mg 5 ml 2 5 ml 2 5 2 5	Soluble in lipid only	4	0 3 $\pm$ 0 65 (S E)
28	Hemin ester Arachid oil	250 mg 10 ml	As study 27	4	10 2 $\pm$ 1 35 (S E)

Chapter IV

Nutritional value of blood proteins

Abstract

If hemoglobin or globin are to be used for food fortification, it becomes necessary to ascertain that the nutritional value of foods so fortified does not become unsatisfactory The chemical score of isolated globin is as low as between 3 and 7 with isoleucin as the limiting amino-acid, and consequently the biological value (25 5) and net protein utilization (25 9) are also low However the true digestibility is high (101 per cent)

During the industrial processing hemoglobin may be frozen bleached or separated into heme and globin. Bleaching may reduce the digestibility and separation may cause the loss of some isoleucin, but these effects seem minor

If cereals are fortified with about 1 5 per cent by weight of hemoglobin (supplying about 15 per cent of the nitrogen) the biological value of the cereals is improved by about 20 per cent. When meat products fortified with 1-10 per cent by weight of hemoglobin (supplying about 4-23 per cent of the proteins) were included in meals, the meals had chemical scores over 90 which is well acceptable

CHEMICAL SCORE

It is known that blood proteins have a relatively low chemical score (FAO 1970 van Kuppevelt et al 1976) The low chemical score is caused by an isoleucin-leucin imbalance This is true both for plasma proteins and, particularly for globin Nevertheless plasma proteins are used extensively in Sweden in making meat products in part for economic reasons, in part because they have favorable physicochemical properties and in part because they make it economically feasible to reduce the high fat content in Swedish meat products

EVALUATION OF FORMULATED FOODS AND PROTEIN EXTENDERS

Gopalan et al (1966 1975) found that under extreme conditions pellagra-like symptoms can be caused by a reduced isoleucin and a high leucin intake This is true both in animals (so-called canine black tongue) and in some pellagra patients

Darby and Hambraeus (1975) have pointed out the responsibility of producers and authorities in studying the nutritional value of formulated foods and protein extenders For this reason the nutritional value of globin was studied (van Kuppevelt et al 1976 Löwgren et al in press)

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Biological value, total digestibility, and net protein utilization of globin Van Kuppevelt et al (1976) performed amino acid analyses of globin prepared by three different preparation methods He could confirm earlier findings of a leucin isoleucin imbalance and he could demonstrate minor losses of some amino acids during preparation

The limiting amino acid in blood protein is isoleucin In contrast blood protein contains reasonable amounts of lysine the limiting amino acid in most cereals For this reason van kuppevelt (1976) also studied the nutritional values of mixtures of cereals and blood proteins

He found the expected low chemical score (between 3 and 10) and biological value (between 21 and 36) in globin and a similarly low net protein utilization (between 18 and 31) However in various protein-cereal mixtures both the chemical scores and the biological values were up to 30 per cent higher than in either blood proteins or cereals alone The optimum was found when 18-20 per cent of the total nitrogen and 1 4-1 7 per cent of the dry weight were derived from blood proteins The possibility of fortification of wheat and other cereals with blood proteins was therefore raised in van Kuppevelt' s article

A similar study was performed by Löwgren et al (in press) who however studied industrially produced blood proteins rather than those produced in the laboratory and realistic composite meals rather than protein-cereal mixtures In these studies also biological values and net protein utilizations were low both for bleached hemoglobin (21 3 and 18 4 respectively) freeze dried red cells (34 7 and 31 4) and for isolated globin (25 5 and 25 9) Total digestibilities were 85 5 90 5 and 101 5 for the three preparations

However all of the three meals studied had a satisfactory chemical score (between 80 and 100) when meat products included in the meals were fortified with up to 10 per cent blood protein The industrially produced blood protein fractions thus did not differ significantly from those produced in the laboratory with the exception of chemically bleached hemoglobin, intended for use as a protein extender Bleached hemoglobin has an apparent but not statistically significantly reduced absorbability

In conclusion, globin and other blood proteins have low nutritional values and are unsuitable as staple foods or main components of diets but well suited to be used as protein extenders in formulated foods and as protein extenders in mixed diets

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By Johan Hulting

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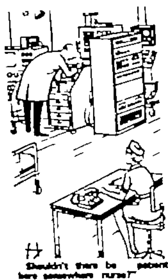
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APPLICATION AND EVALUATION OF AUTOMATED ARRHYTHMIA MONITORING IN THE CORONARY CARE UNIT

Johan Bulting



Shouldn't there be patient here somewhere nurse?"

This thesis is based mainly on the following papers

I Hulting J & Nygårds M -E Evaluation of a computer-based system for detecting ventricular arrhythmias Acta Med Scand 199 56-60 1976

II Hulting, J Blomqvist P & Nygårds M -E Computer-based ECG analysis in acute myocardial infarction A comparison between two computer programs for the detection of ventricular arrhythmias Acta Med Scand 201 439-447 1977

III Hulting, J & Nygårds M -E Accuracy of alarms from a computer-based arrhythmia monitoring system Acta Med Scand 203 153-159 1978

IV Hulting J Detection of asystole ventricular fibrillation and ventricular tachycardia with automated ECG monitoring Acta Med Scand (accepted for publication)

V Nygårds M -E & Hulting J A system for automated ECG monitoring Comp Biomed Res (accepted for publication)

VI Hulting J Arrhythmias in the coronary care unit recognized with the aid of automated ECG monitoring A twelve-month study in 679 patients Acta Med Scand (submitted for publication)

The above papers will be referred to by their Roman numerals I - VI

CONTENTS

ABBREVIATIONS

AMI	Acute myocardial infarction
BBB	Bundle branch block
CCU	Coronary care unit
ECG	Electrocardiogram electrocardiographic
HR	Heart rate
PVB	Premature ventricular ectopic beat
SR	Sinus rhythm
SVB	Supraventricular ectopic beat
SVT	Paroxysmal supraventricular tachycardia
VB	Ventricular ectopic beat
VF	Ventricular fibrillation
VT	Ventricular tachycardia

DEFINITIONS

This text contains terms used in medical computer technology Definition and explanation of some terms have been collected below

Algorithm A set of rules for the solution of a problem in a finite number of steps

Analog computer technique Computational quantities represented by physical quantities usually voltages

Arrhythmia detector Central part of an arrhythmia monitoring system Analyses each waveform of the incoming ECG signal The detector produces notes regarding specific events in the ECG or information regarding the present state of the signal e g heart rate background rhythm and artefacts

Basis functions representation Representing a whole class of functions with its inherent components When added together with proper amplitudes these components or basis functions will reproduce any member of the class

Digital computer technique Computational quantities represented by binary numbers

Discriminant function analysis Statistical technique for studying differences between populations Can also be used to learn which combination of measurements best separates the populations

Monitoring system Administrates stores and presents data generated by one or more arrhythmia detectors

Orthonormal basis functions Basis functions which are both orthogonal and normal i e the average product of corresponding points in any pair of different functions should be zero, whereas the average product of any function with itself should be unity

Power spectrum The power of a signal computed for each frequency component within the signal

INTRODUCTION

Acute myocardial infarction (AMI) is an important cause of morbidity and mortality AMI was associated with a hospital mortality between 16 and 34% in a Swedish multicenter study (Henning & Lundman 1975) However a significant proportion of patients with AMI die suddenly before reaching the hospital (Wikland 1971) Unexpected deaths in or outside hospital are usually caused by arrhythmias probably ventricular fibrillation (VF) (Lown et al 1969 Liberthson et al 1974) This and some other serious arrhythmias can be reverted to normal by electric countershock as demonstrated by Zoll et al (1956) and Lown et al (1962) For proper treatment of arrhythmias the ECG must be available Continuous ECG monitoring of cardiac patients and active treatment of arrhythmias were introduced in the early 60 s (Day 1963 Brown et al 1963 Julian et al 1964 Meltzer & Kitchell 1966) Two controlled studies have shown that such coronary care in AMI lowered the hospital mortality about 50% and this reduction was statistically significant (Christiansen et al 1971 Hofvendal 1971) The beneficial effect of treatment in a coronary care unit (CCU) compared to treatment in ordinary hospital wards remained significant up to three years after discharge from hospital (Hofvendal 1971)

Conventional ECG monitoring in the CCU utilizes bedside amplifiers and oscilloscopes that are connected to multichannel visual displays centrally Optimally the nurses perform round the clock surveillance of oscilloscope screens but personnel resources usually do not permit constant human observation Even so it is obvious that attention fluctuates markedly during the day To improve the ECG monitoring heart rate (HR) alarms have been added The ratemeter alarm alerts the staff when HR deviates outside preset limits The HR alarm system usually detects the most serious arrhythmias such as asystole and VF

In some patients signal artefacts including muscle potentials give rise to numerous false tachycardia alarms Frequent false bradycardia alarms occur in patients with low amplitude ECG complexes Also the HR system is insensitive to brief slow or fast rhythm changes due to a built-in time constant Neither a sudden conduction disturbance nor a rhythm change that falls within the HR limits of the system is detected The efficiency of the HR system alone in ECG monitoring has not been critically evaluated In one report only 10 out of 167 HR

Discriminant function analysis   Statistical technique for studying differences between populations Can also be used to learn which combination of measurements best separates the populations

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alarms observed during 200 h of monitoring were true tachy- or bradycardia alarms (Frost et al 1977) The HR alarm system usually activates a paper chart recorder presenting the ECG at an alarm but because of the time constant this record never shows the initial part of the alarm-generating event Therefore most manufacturers have incorporated a memory loop into their system Constant recording and erasing of the ECG from each patient in the unit is performed At an alarm the ECG preceding the alarm can be presented A better method for arrhythmia documentation is a slow speed continuous ECG recording from all patients in the CCU with the use of a multichannel recorder (MacMillan et al 1967 Mogensen 1970) However a thorough analysis of all the data produced is very time-consuming

The accuracy of routine nurses-based arrhythmia monitoring has been tested in a few studies (Mogensen 1970 Romhilt et al 1973 Lindsay & Bruckner 1975 Vetter & Julian 1975, Holmberg et al 1977) The methods used for establishing the true arrhythmia incidence and prevalence as well as the length of the test periods differed markedly between the investigators Thus it is difficult to compare the abovementioned studies Mogensen (1970) found that the nurses detected about 25% of all episodes of ventricular tachycardia (more than 2 ventricular ectopic beats (VBs) in succession with a rate >100/min) and about 50% of all patients with this arrhythmia during the first 24 h in the CCU A similar observation was made by Ryden et al (1975) Romhilt et al (1973) showed that conventional monitoring detected about 20% of the patients fulfilling criteria given by Lown et al (1967) for prophylactic treatment with lidocaine in order to prevent VF in AMI Also there was a marked time delay between the first true arrhythmia episode and the first arrhythmia detected by the nurses

A proper quantification of arrhythmias is difficult with the conventional oscilloscope monitoring technique This can be a disadvantage in antiarrhythmic treatment Even though memory oscilloscopes are now used in many CCUs the time available for the human observer may be too short to permit an accurate arrhythmia diagnosis The constant observation of oscilloscope screens is boring and probably one important reason for the difficulties in recruiting nurses to the CCU High quality conventional monitoring is expensive since it requires a large and well trained staff

The need for improved methods for arrhythmia monitoring has been emphasized earlier (DeSanctis et al 1972 Fozzard 1973 Vaisrub 1975) In order to improve the standards of ECG monitoring and to reduce the monitoring demands on the staff great efforts have been made to develop automated monitoring systems Such systems based on digital computer technique also permit rational methods for the storage and presentation of data

In this study a computer-based arrhythmia monitoring system for the CCU will be presented and discussed The present version of the system installed in the CCU of Södersjukhuset Stockholm has been developed in close co-operation with the Department of Medical Information at Linköping University

The present monitoring system constitutes one part of a larger project for the application of computers in clinical medicine The work on

ECG monitoring was commenced in 1970 A QRS detector based on analog technique was constructed in 1972 The principles for arrhythmia detection were implemented into a digital computer in the following year The various stages during development and evaluation are shown in Fig 1

The aim of the present study may be summarized as follows:

1 To present and discuss the development of an automated arrhythmia monitoring system for the CCU (I II and V)
2 To evaluate this system in various arrhythmias occurring during CCU monitoring (III and IV)
3 To use the automated monitoring system as an aid for the study of arrhythmias in a large number of CCU patients (VI)
4 To improve knowledge regarding the clinical relevance or prognostic value of arrhythmias detected by the system (VI)

Computer-assisted analysis of ambulatory ECG recordings and automated arrhythmia interpretation of the diagnostic ECG are not within the scope of this study

alarms observed during 200 h of monitoring were true tachy- or bradycardia alarms (*Frost et al 1977*) The HR alarm system usually activates a paper chart recorder presenting the ECG at an alarm but because of the time constant this record never shows the initial part of the alarm-generating event Therefore most manufacturers have incorporated a memory loop into their system Constant recording and erasing of the ECG from each patient in the unit is performed At an alarm the ECG preceding the alarm can be presented A better method for arrhythmia documentation is a slow speed continuous ECG recording from all patients in the CCU with the use of a multichannel recorder (MacMillan et al 1967 Mogensen 1970) However a thorough analysis of all the data produced is very time-consuming

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SPECIAL PURPOSE ARRHYTHMIA DETECTORS

In the special purpose arrhythmia detector all signal analysis is performed in electronic circuits specially designed for this purpose and serving one patient at a time Depending on the function of these circuits various characteristics of the signal may be recognized and used for beat separation and classification Detector output is either proportional e g to HR or in the form of electric impulses e g one for each VB detected by the system Most of the older detectors work with analog technique Some of the monitors are hybrid performing both analog and digital signal processing

The simplest special purpose detector is the HR-meter In the process of improving the ratemeter the early work by Haber (1959) resulted in an arrhythmia detector that recognized abnormal beats from changes in HR and prolongations in the QRS interval Others performed arrhythmia analysis and classification solely on the basis of R R interval analysis (Nacher et al 1971 Stinton et al 1972 Rompelman et al 1977 Fantem et al 1977) The difference in QRS area between an adaptive reference complex and each new waveform was used in an arrhythmia detector constructed by Neilson (1974) Kezdi et al (1968) separated normal and abnormal beats by a cross correlation technique Detection of aberrant beats by comparing the energy content of two frequency bands of the ECG signal has been devised and evaluated by Karlsson et al (1970) A method for the detection of early VBs (R-on-T VBs) has been described (Breithardt et al 1975) but there are no data as to its usefulness in clinical monitoring A small portable analog detector suited mainly for use in ambulatory patients was described and tested by Cannon & Harrison (1974) Feezor et al (1970) developed a waveform analyzer in which abnormal beats were identified from amplitude criteria In order to separate VBs from other beats and artefacts abnormal beats were correlated with a fixed VB waveform stored in the system However no acceptable testing of this detector has been published This lastmentioned principle for arrhythmia analysis was implemented into the first version of the present arrhythmia monitor

Although several special purpose detectors have been used in clinical practice they ha e not reached general acceptance There are probably several reasons for this Firstly various arrhythmias and

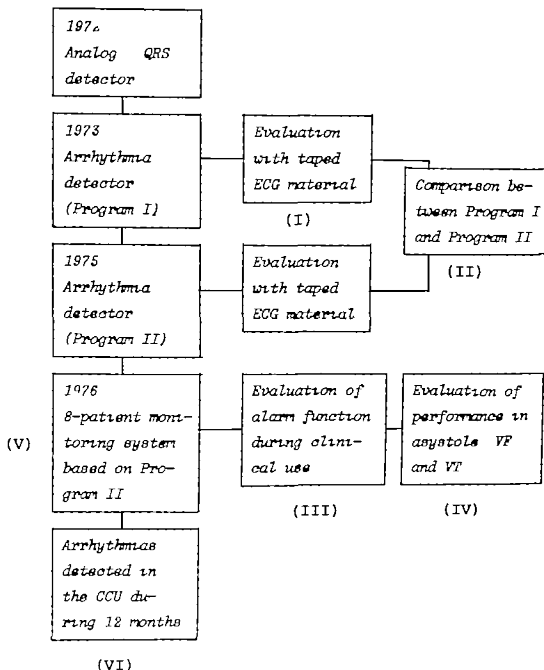


Fig. 1 Various stages during system development and evaluation

COMPUTER PROGRAMS FOR ARRHYTHMIA DETECTION

The small digital computer (minicomputer) with its flexibility great computational capacity and relatively low price has opened the field for advanced arrhythmia monitoring in the CCU Also one computer may analyse the ECG from several patients simultaneously The initial expectations however were too optimistic and progress during the last decade has been relatively slow Early algorithms that worked in the laboratory did not perform equally well during routine CCU monitoring

In the digital systems the ECG signal is sampled with a rate between 100 and 500 Hz Methods for the reduction and the detection of artefacts have been omitted from this brief description In the next stage of the analysis QRS detection is performed usually from the derivative of the signal (first difference of sample points) A possible QRS complex can be handled in several different ways Some systems perform a direct comparison/correlation with a stored normal for the patient In other systems certain characteristics (features) from each complex are extracted In Table I the principles for some arrhythmia detectors and monitoring systems described and evaluated in the scientific literature are presented For proper functioning of the detector the stored normal waveform must adapt itself to slow spontaneous changes in the shape of the ordinary QRS complexes Abnormal complexes may be correlated to previously detected and manually classified beats (Feldman et al 1971) to a fixed stored prototype VB waveform (Wigertz et al 1974) or to previously detected and stored families of abnormal complexes (Shah et al 1977) This correlation aims at a seberation between normal beats SVBs VBs and various artefacts Hultgren et al (1975) evaluated a monitoring system which separated abnormal beats from normal ones with the use of a correlation technique and/or R-R analysis

In most detectors and monitoring systems in Table I some kind of data compression is performed in order to make it possible to handle the enormous amount of data that is fed into the computer A useful data reducing preprocessing algorithm reported by Cox et al (1968) has reached wide-spread use With this algorithm called Aztec (amplitude-zone-time-epoch-coding) the ECG signal is transformed into

artefacts in clinical monitoring are too variable to be handled satisfactorily by these relatively simple devices As a consequence results from thorough evaluations are lacking for most detectors and no long-term clinical evaluation study has been presented, with the exception of a study by Vetter & Julian (1975) This will be referred to on page 50 Secondly most special purpose detectors rely on individual control of parameter settings This puts unacceptable demands on the staff in a multipatient system

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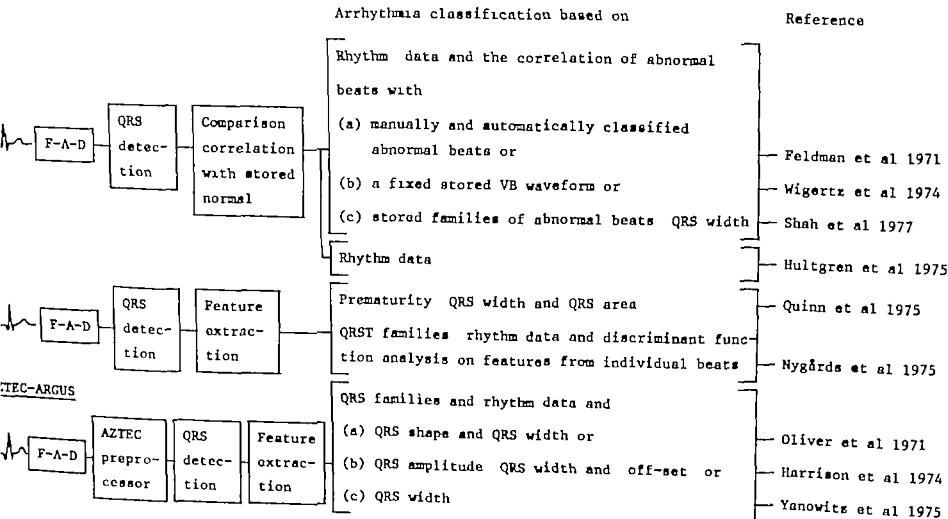
horizontal lines and slopes In the further analysis each complex is characterized with respect to amplitude width and shape In a following step complexes with similar shapes are grouped together In the final classification of a complex rhythm data such as prematurity and compensatory pause are also considered The above principles of arrhythmia detection (ARGUS Arrhythmia Guard System) have been implemented into some systems (Oliver et al 1971 Harrison et al 1974 Ianowitz et al 1974) A modified Argus system has been described by Zeelenberg et al (1977) Other features that have been used in arrhythmia detectors are QRS width and QRS area (Quinn et al 1975) An effective method for feature extraction should allow adequate waveform characterization with a minimum of parameters In the final version of our own monitoring system the method used made it possible to represent the entire QRST complex from five parameters (7)

Ideally a monitoring system should work with a minimum of operator (nurse) interference The method should be relatively insensitive to minor or moderate disturbances in the ECG signal occurring during clinical monitoring

The great variability in rhythms beat shapes and artefacts calls for modifications of arrhythmia algorithms during the developmental stage Such changes in the programs must rely on thorough evaluation studies Changes in one part of the program however may add new problems to other sites

2

le I Principles for some digital arrhythmia detectors and monitoring systems F-A-D = Filtering and artefact ucing steps and analog to digital conversion

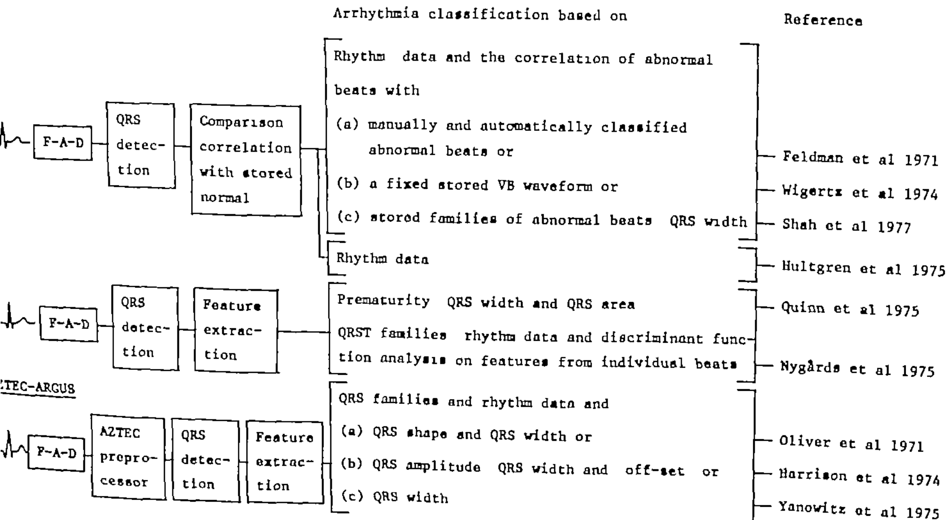


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ARRHYTHMIA DETECTOR AND MONITORING SYSTEM EVALUATED IN THE PRESENT STUDY

The two methods for arrhythmia analysis in the CCU used in the present study will be described in some detail and complement the principal aspects mentioned in the previous section

VENTRICULAR BEAT (VB) DETECTION BY CORRELATION OF ABNORMAL BEATS WITH A FIXED VB WAVEFORM (PROGRAM I)

A 16-bit minicomputer (Datasaab D5/30) with 16 K words of core memory was used in the first arrhythmia detector The arrhythmia program provided a beat-by-beat real-time analysis of the ECG The program organization is illustrated in Fig 2

Sampling and R wave recognition The sampling program had the highest priority and was executed every 10th ms After digital low pass filtering (30 Hz cut off) the differences between sample points of the ECG were computed and stored in a circular memory of 512 8-bit words Artefact detection was also performed and permitted automatic rejection of low-quality ECG portions Whenever the derivative of the ECG signal or a base line shift exceeded certain limits the waveform analysis was blocked for 2 s R wave recognition was performed using

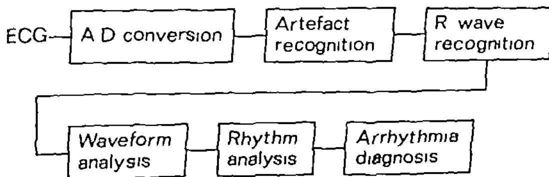


Fig. 2 Program organization in the first arrhythmia detector

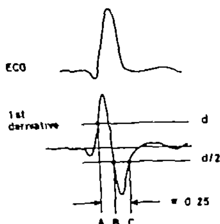


Fig. 3 Principles for R wave detection (Program I and II) For explanation of symbols see text



Fig. 4 Prototype VB waveform (Program I)

an adaptive threshold (d) for the difference between sample points An R wave was detected when the following sequential criteria were fulfilled within 0 25 s: (A) positive difference exceeding threshold (d) (B) negati e difference exceeding threshold (d/2) (C) signal returning to base line or difference below threshold (d/2) (Fig 3) At the detection of an R wave the previous R-R interval and the position in the memory were passed to the waveform analysis program

Waveform and rhythm analysis. For each R wave 200 ms of sampled data were compared to the running average of the normal QRS complex for the patient This reference complex was created at the onset of monitoring from the first 10 s of the ECG A new complex was considered normal if the sum of absolute differences between corresponding sample points went below a certain limit A beat classified as normal was added to the running average with a time constant corresponding to 32 beats To separate VBs from artefacts and beats of supraventricular origin each abnormal complex was

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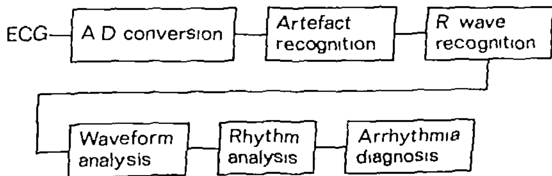


Fig. 2 Program organization in the first arrhythmia detector (Program I)

described However the inhibition of the analysis at a high level of artefacts was extended from 2 to 4 s

A waveform recognized as a possible R wave was analysed further and classified into one of the following categories: normal beat supraventricular beat (premature) ventricular beat undefined beat or artefact This procedure involved the following steps: feature extraction grouping of waveforms shape classification and final diagnosis

Feature extraction. The QRST complex was represented as the sum of four approximately orthonormal basis signals The basis signals two for the QRS and two for the ST part of the complex were mathematically represented by the Gaussian function and its first derivative (Fig 6) In addition QRS width was computed whereas the distance between the QRS and the ST was predicted from HR according to Bazett (1920) Consequently five parameters were used to describe the morphology of each complex: the QRS width and the amplitudes of the four basis signals The mean square error between the sample points of the original complex and the curve reconstructed from the parameters was

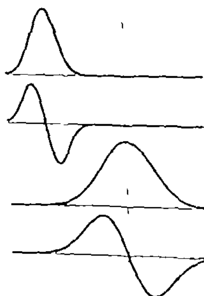


Fig. 6 Basis signals used for QRST representation (Program II)

correlated to a typical VB waveform (Fig 4) which had been derived from earlier ECG recordings An abnormal complex was marked as ventricular if the absolute value of the normalized correlation coefficient between the complex and the stored VB exceeded 0 8 If the basic rhythm was regular a waveform approved as ventricular was classified as a VB only if preceded by an R-R interval shorter than 90% of the running average and followed by a compensatory pause The basic rhythm was considered regular if the running standard deviation of R-R intervals was less than 8% of the average R-R interval

The above arrhythmia detector was tested on a taped ECG material (I) and also compared with a more complex method for arrhythmia analysis (II) Program I was implemented into a 4-patient monitoring system in 1974 This system however was not taken into routine use

ARRHYTHMIA CLASSIFICATION WITH THE USE OF QRST BASIS FUNCTIONS AND POWER SPECTRUM OF THE ECG (PROGRAM II)

The program organization is shown in Fig 5

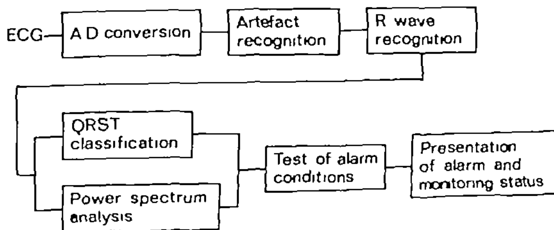


Fig. 5 Program organization in the second arrhythmia detector (Program II)

Signal filtering and sampling rate were the same as in Program I R

normal beat or if premature as a SVB with normal shape The classification of an abnormal beat was considered preliminary until the next beat had been recognized

Final diagnosis In this step prematurity and compensatory pause were combined with the shape classification The final diagnosis was also influenced by basic rhythm and by the number of complexes in an abnormal waveform group as well as by the error in the parameterization procedure The tests for prematurity and compensatory pause rested on a statistical basis utilizing the running average and covariance of R-R intervals of normal complexes To further improve artefact suppression an index reflecting noise level was computed This index was incremented at a failure of the parameterization and each time a new waveform group was created Also an excessive baseline shift between adjacent QRST complexes added to the index which gradually returned to zero at the detection of undistorted normal beats At a certain value of this index the classification of abnormal beats was blocked

Power spectrum analysis A special subroutine to aid the recognition of VF VT and asystole was entered at the detection of an abnormal ECG pattern lasting for 5 s in a signal free from major artefacts This subroutine computed the power spectrum of the ECG Asystole was diagnosed if the power of the signal did not exceed a certain limit and if no R waves had been detected during 5 s VF and VT were differentiated from other conditions by searching a peak in the power spectrum between 1 7 and 9 Hz If such a peak was found VT and VF were diagnosed from the peak frequency and the relative power of a frequency band including the peak

AN AUTOMATED ARRHYTHMIA MONITORING SYSTEM BASED ON PROGRAM II

System configuration

Program II was incorporated into an 8 patient arrhythmia monitoring system that was gradually introduced to the personnel in 1976 The general configuration of the system is shown in Fig 7 An extension of core memory of the minicomputer from 16 K to 28 K was necessary in order to allow multipatient monitoring Interactive procedures and

computed in order to estimate the precision of each parameterization If this error exceeded a certain value the original complex was regarded as an artefact In a later version of the program, however a fifth basis signal corresponding to the second derivative of the Gaussian function was added to the original set when parameterization failed This fifth basis signal was introduced in order to obtain a better representation of a QRS complex with a split R wave

Waveform grouping Complexes with similar shapes as described by the waveform features were brought together Each waveform group was characterized by the means and the standard deviations of five parameters transformed from the original set of four amplitude coefficients and one width parameter The reference group comprised the waveform that dominated when monitoring was initiated The grouping of subsequent beats was based on a distance measure in the five-dimensional feature space A new group was created when the distance to the existing group(s) exceeded preset limits However a new group was considered preliminary until the number of complexes reached a certain threshold that was dependent on the noise level and the degree of shape aberration The parameters of a complex were updated whenever a new complex was incorporated A maximum of eight groups was allowed for each patient Adjacent groups were put together at regular intervals and a group without new complexes during a certain period of time was deleted To cope with sudden changes in the shape of the reference complex this was substituted for the presently dominant group if no new complexes had been assigned to the former group for about 2 min If the difference between the new and the old reference waveform exceeded certain limits a message was delivered

Preliminary waveform typing Waveforms not assigned to the reference group were separated into four categories probable VBs possible VBs abnormal non-VBs and essentially normal complexes This classification was based on two linear discriminant functions operating on the features of the current waveform and if the rhythm was regular on the preceding R-R interval The coefficients of these functions were set to minimize the probability of misclassification in a previous ECG material This material was equivalent to that described earlier (I) A complex belonging to the reference group or classified as essentially normal in the above procedure was typed as a

return of power the system was automatically restarted

Alarm conditions

At the detection of an abnormal ECG a number of alarm tests were performed In Table II the various alarms associated with arrhythmias are listed and defined Alarm limits for bradycardia tachycardia and VB excess rate could be set individually but were automatically set to 50 120 and 5/min repectively at the onset of monitoring Alarm messages referring to the status of the ECG signal are shown in Table III The alarm what has happened? however was reported at the detection of an abnormal ECG that fitted neither the criteria for noise nor those for an arrhythmia alarm

Status and alarm presentation

The upper part of the video screen was used for displaying HR VB frequency basic rhythm and alarm messages for each patient (Fig 8) Alarms could be reset from bedside or the central station but automatic reset was performed after a certain time (usually ½ min) if the alarm condition was no longer present The alarms were grouped into three priority levels

(1) Highest priority or *** alarms These messages resulted in a repetitive signal in the pocket receiver and a flashing red light at the bedside and in the central station

(2) Second priority or ** alarms which were accompanied by a short sound and a steady light

(3) Lowest priority or * alarms These messages were presented on the video screens without any additional alerting signals

At arrhythmia alarms a write-out with an ECG signal delayed 5 s was recorded automatically at a speed of 10 mm/s and usually with a duration of 15 s

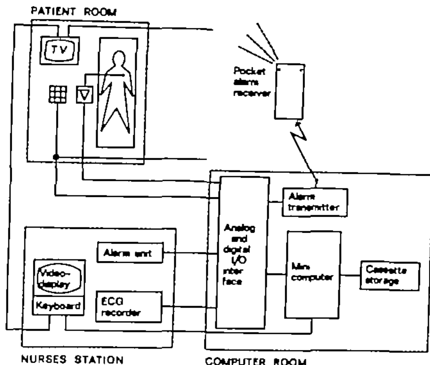


Fig. 7 Configuration of the monitoring system

data storage A bipolar ECG with fixed amplification was obtained from standard bedside equipment Monitoring on/off and alarm reset controls were added to existing patient units Monitoring status and arrhythmia alarms were presented on a video terminal in the nurses station with slave monitors in the patient rooms A computer-controlled 2-channel ink-jet recorder in the central station was used to document the ECG causing an alarm A wireless alarm transmitting system controlled by the computer was activated in special alarm situations and alerted the nurses who carried small pocket receivers Interactive communication with the monitoring system was performed via the video terminal or handheld numeric keyboards at bedside

All programs were loaded from a cassette tape unit However in case of power failure the content of the core memory remained intact and on

Table III Monitoring status alarms

Priority	Message	
**	WHAT HAS HAPPENED?	Abnormal patt rn for 10 s in the absence of art facts and no other condition applicable
**	CHECK LEADS	High level of artefa ts for 30 s monitoring impossible
**	NEW QRS	New shape of r ference complex rhythm unchanged
*	NOISY ECG	VB d tection inhibited due to artefacts for at least 15 s of last min
*	CHANGE ELECTRODE PLACEMENT	Peaked P or T waves or narrow Q or S waves VB dete tion inhibited
*	LOW AMPLITUDE	Amplitude of normal QRS<0 3 mV VB d te tion inhibited
*	BAD ELECTRODE CONTACT	Pow rline interf rence



Fig. 8 Status and alarm display On the upper part of the screen are shown name HR (HFR) number of VBs (VES) during last minute and rhythm (RTTM ORREGELB irregular) for each patient Alarm messages appear to the right Present display shows alarms for multiform VBs (patient 3) and more than 5 SVBs/min (FLER AN 5 SVES/MIN) from patient 7 Below is seen a trend plot from patient 3 with HR and VB frequency for the last 23 h

Table II Arrhythmia alarms

Priority	Message	Explanation
***	ASYSTOLE	R-R >5 0 s and power below threshold
***	VENTRICULAR FIBRILLATION	Abnormal pattern for 5 s and peak in power spectrum
***	VENTRICULAR TACHYCARDIA	More than 3 consecutive VBs and rate >120/min or narrow peak in power spectrum
**	RUN OF MORE THAN 3 VB S	More than 3 consecutive VBs with rate ≤120/min
**	IDIOVENTRICULAR RHYTHM	More than 3 consecutive VBs with rate ≤40/min or QRS width >0 14 s and HR ≤40/min
**	BRADYCARDIA	HR more than 15 beats/min below bradycardia limit
**	TACHYCARDIA	HR more than 30 beats/min above tachycardia limit
**	RUN OF 2-3 VB S	2 or 3 consecutive VBs
**	R-ON-T VB S	2 early VBs of the same shape within 15 min
**	VENTRICULAR BIGEMINY	3 VBs alternating with normal beats
**	SUPRAVENTRICULAR TACHYCARDIA	More than 3 consecutive SVBs with a rate above tachycardia limit
*	MORE THAN 5 VB S/MIN	
*	MULTIFORM VB S	2 differently shaped VBs within 5 min
*	MISSING QRS	R-R interval between normal beats at least 50% prolonged on two occasions during the past min and basic rhythm regular
*	MORE THAN 5 SVB´S/MIN	
*	BRADYCARDIA	HR below bradycardia limit (normally 50/min)
*	TACHYCARDIA	HR above tachycardia limit (normally 120/min)

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Table IV Interactive procedures

Enter/discharge patient
Display/change alarm limits
Select ECG write-out mode
Trend diagram for last 6 min/last hour/last 24 hours
Start/stop ECG recorder
Start/stop ECG monitoring
Reset alarm
Enter date and time
Review alarm messages
Inactivate VB monitoring
Check alarm signals

Interactive procedures

As shown in Table IV these procedures included i e change of alarm limits for HR trend diagrams over HR and VB frequency (Fig 8) and screening of stored alarms Interactive routines were displayed on the lower part of the screens all showing the same picture Thus communication with the computer except for monitoring on/off and alarm reset was only possible from one terminal at a time

DISCUSSION

In the development of our own system two methods for beat discrimination and classification have been used The feature extraction method (Program II) was found to be more flexible permitting a differentiation between ventricular and supraventricular beats The algorithm for determination of power spectrum was developed simultaneously with the feature extraction method but could have been implemented in Program I as well

So far most CCU monitoring systems rely only on one bipolar lead However the possible advantage of introducing two chest leads has been preliminarily tested for out-patient monitoring (Clark et al

1977 Nolle et al 1977) A few arrhythmia detectors use intracardiac or oesophageal leads in order to obtain an acceptabel P wave detection (Bernard et al 1977 Lorente et al 1977 Jenkins et al 1978) Intracardiac leads impose a risk to the patients and also put extra demands on the CCU staff which explains the restricted clinical application of such systems

The sampling rate used in our program (100 Hz) is lower than that used in most other systems but has been found sufficient for arrhythmia monitoring

The monitoring system was designed for maximal flexibility with regard to the presentation of alarms and interactive communication Thus all interactive procedures except entering the patient s name could be performed from the bedside Most other current monitoring systems only permit full communication from the central station The wire-less alarm system which up to now is a unique feature has been incorporated in order to enable the nurse to move around freely with little risk of overlooking an essential arrhythmia The graded alarm function was also important to minimize interference with other nursing activities The ranking and selection of arrhythmias in the various priority groups were made on empirical grounds It was assumed: (1) that a highest priority alarm often required immediate action from the nurse; (2) that the second priority alarms should be recognized but usually did not require immediate action and (3) that the lowest priority alarms could be of importance but did not require active alerting A similar philosophy for alarm grading has been described by Sanders et al (1975)

The arrhythmia write-outs have been necessary for documentation Only one small oscilloscope in the central station was available for ECG presentation from a selected patient The write-out with its alphanumeric printing made long term clinical evaluation of the system possible

The monitoring status alarms were introduced to aid the nurse in finding an acceptable ECG complex with a low noise content

EVALUATION OF THE PRESENT ARRHYTHMIA DETECTOR AND MONITORING SYSTEM

PRINCIPAL ASPECTS ON EVALUATIONAL PROBLEMS

A number of arrhythmia monitoring systems have been described in th last 10 years and in the last 2-3 years the number of commercia installations has grown rapidly This development has taken plac without documentation regarding the performance of the arrhythmi detector or the monitoring system in clinical long-term rhyth surveillance For most systems short-term performance in selecte patients has been reported but such results cannot be directly applie to long-term monitoring in the clinical setting

All evaluation studies presented so far are based on test materia collected by each investigator The methods for evaluation may diffe widely and have not always been adequately specified In evaluatin the performance of the detector it seems rational that each complex i referred to the true diagnosis In this study as well as in most other similar investigations the results of the beat-by-beat evaluation have been expressed in the following terms

$$\text{Correct (VB) detections} = \frac{\text{No of correct (VB) detections}}{\text{Total no of beats (VBs)}}$$

$$\text{False negative (VB) detections} = \frac{\text{No of missed or incorrect (VB) detections}}{\text{Total no of beats (VBs)}}$$

$$\text{False positive (VB) detections} = \frac{\text{No of ordinary or other ECG events classified as abnormal beats (VBs)}}{\text{Total no of ordinary beats}}$$

In the present studies various aspects of importance for the evaluation and comparison of arrhythmia detectors will be considered Performance may differ in regular compared to irregular rhythm The methods for beat separation and classification may work better or worse depending upon the beat configurations The incidence of

arrhythmias may be important since a few systems suppress the detection of sporadic VBs The characteristics of the ECG signal are extremely important and include i e the level and type of artefacts QRS amplitude beat shape variations and P and ST amplitudes in relation to the QRS All the above factors are dependent on the ECG material and thus on the principles for ECG data collection In addition the reference interpretation by the cardiologist(s) is subjected to variation The computer diagnosis should not be known to the interpreter but still classification may vary depending on the experience of the cardiologist(s) on the diagnostic criteria used and on the interpreter s knowledge of the principles for automatic classification Two or more independent interpreters would be an advantage but could also complicate the typing of complexes when opinion differs

From what has been said above it is obvious that the performance of the arrhythmia detector is influenced by a great number of circumstances and a proper comparison of different arrhythmia detectors would require a common ECG data base Such a data bank has been proposed (Feldman 1974 Ripley & Arthur 1975 Zeelenberg et al 1977 Ripley & Oliver 1977), but so far no generally available ECG material has been collected

The evaluation of a complete monitoring system in clinical routine imposes some special problems Interaction with the system such as a change of alarm limits or criteria for arrhythmia classification will modify the results Also a change of lead placement or signal characteristics will affect the performance Long term evaluation during routine monitoring will be less vulnerable to a biased selection of patients provided no exclusions are made An independent beat-by beat interpretation of the ECG during routine use is laborious as well as the comparison between the manual and the automated interpretation Therefore long term arrhythmia evaluation should preferably concentrate on the performance in special alarm situations However there is no general agreement as to the definition of various arrhythmias or as to the most relevant arrhythmias to monitor in the CCU The performance of the system in special alarm situations can be presented principally in two ways (Holting et al 1977) Thus the performance of the system in each type of alarm reported by the system may be analysed (cf Fig 10) or the performance of the

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Dr A \ Dr B	V	A	N	O	X
V	I	II		III	
A					
N			IV		VI
O		III		V	VI
X				VI	VI

Fig. 9 Diagram used for the assessment of final beat diagnosis and for comparison between interpretation by the computer and the physicians After classification by the physicians (V probable VB; A possible VB; N aberrant beat probably non-VB O ordinary beat or SVB with normal shape and X artefact) an abnormal complex or event was located to one of the 6 areas: I VB II suspected VB; III divergent opinion between the physicians IV abnormal non-VB; V ordinary complex (false VB); and VI artefact (false VB) VB classification by the computer was indicated in the upper left triangle of each square and computer non-VBs were marked in the lower right triangle

Tabl V Comp ison betw en l ssificat on in p tients with sinus rhythm (SR) and t ial fibrill tion (A fib) P rcentage compute VBs within pa enthes s

Phy i ians	VB		Suspec- ted VB		Div gent int rpre- tation		Abnormal compl x Non-VB		Nor- mal	Arte f ct
Comput r	VB	Non-VB	VB	Non-VB	VB	Non VB	VB	Non-VB	VB	VB
SR	726 (98)	15	328 (86)	53	23 (20)	94	14 (8)	159	1	33
A fib	496 (88)	69	183 (51)	179	29 (28)	75	112 (33)	226	71	7

reference to the true arrhythmia diagnosis may be studie (cf Fig 11 12 and 13)

In some following sections monitoring in various arrhythmias will b described Some other aspects of automated ECG monitoring will b discussed on pp 62-67

EVALUATION OF PROGRAM I

A bipolar ECG from 15 patients with ventricular arrhythmias was recorded on tape in order to evaluate the performance of Program I The material was also reproduced on paper at a speed of 10 mm/s and evaluated independently by two CCU physicians who had no prior knowledge of the computer diagnosis and only briefly knew the principles for arrhythmia classification used in the computer algorithms All abnormal beats and artefacts were numbered and classified No particular diagnostic criteria were agreed upon in advance The final diagnosis of a complex was established with the use of a special diagram (Fig 9)

Results The duration of the recordings varied between 5 and 85 min A total of 53 260 complexes was analysed out of these 2 781 or 5 2% were considered abnormal by the physicians If all beats finally classified as definite VBs or "suspected VBs were put together a correct classification was seen in 85% of all VBs In individual patients the values ranged from 39 to 100% The average number of false positive VB detections amounted to 0 45% of the total number of complexes in individual patients the values ranged from 0 00 to 2 70% Six of the 15 ECG recordings were from patients with atrial fibrillation The results of the analysis in sinus rhythm (SR) and irregular rhythm were compared (Table V) The percentage of correctly classified VBs was higher in SR as compared to atrial fibrillation The proportion of beats referred to the groups with suspected VBs divergent interpretation and abnormal non-VBs was higher in atrial fibrillation The percentage of normal beats falsely reported as VBs in atrial fibrillation was 0 30 the corresponding figure in SR was 0 003 The most important reasons for false negative detections were absence of prematurity/compensatory pause and narrow QRS/low correla-

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T bl V Comp r son b tween l ssifi ti n in patients with sinus rhythm (SR) and at ial fib ill ti n (A fib) P centage computer VB w thi pa entheses

Phys ans	VB		Suspec-ted VB		Divergent interp e-tation		Abnormal complex Non-VB		Nor mal	Arte-fa t
Comput	VB	Non-VB	VB	Non-VB	VB	Non VB	VB	Non-VB	VB	VB
SR	726 (98)	15	328 (86)	53	23 (20)	94	14 (8)	159	1	33
A fib	496 (88)	69	183 (51)	179	29 (8)	75	112 (33)	226	71	7

tion with the prototype VB False positive detections usually resulted from narrow ectopic beats or essentially normal beats with amplitude variations Electrode problems or signal noise were not frequent causes of false positive VB detections

Comments. Provided that the incidence of arrhythmias as well as the performance of the arrhythmia detector were constant during the test period it could be shown that the percentage of correctly detected VBs would fall in the interval between 82 and 90% if the total monitoring time the total number of complexes or the total number of abnormal beats had been standardized in all test records Average monitoring time in patients with atrial fibrillation and SR was almost identical Three patients were also included in a set of learning ECGs used for improvement of the classification rules The result of the arrhythmia analysis in these three patients was slightly less favourable compared to the rest Thus the use of varying lengths of the ECG records etc probably did not introduce any bias into the results

In the evaluation of Program I a few drawbacks of the monitoring method became apparent The prototype VB waveform showed low correlation with bi- or tri-phasic ventricular complexes On the other hand, in patients with a QRS interval wider than normal and particularly in left bundle branch block (BBB) the fixed VB and ordinary complexes showed a good congruence resulting in false positive VB detections Therefore a more flexible scheme for arrhythmia analysis was developed (Program II) The coefficients in the discriminant functions used for preliminary classification of waveforms in Program II were set to obtain an optimal performance of Program II in the ECG material used in the evaluation of Program I

COMPARISON BETWEEN PROGRAM I AND PROGRAM II

The relatively simple correlation technique used in Program I was compared with the more elaborate method for arrhythmia classification used in Program II (II)

A routine bipolar ECG from 12 patients with AMI was recorded on magnetic tape The recordings were started 2-8 h after the onset of symptoms and lasted for 12 h except for one patient who died after 10

b A paper recording of the ECG (12 5 mm/s) was scrutinized minute by minute by the author who had no knowledge of the results of the computer analysis The manual classification was based on prematurity QRS width aberrancy and P wave information (if present) Only VBs were marked and in the case of difficulties in separating a possible VB from a possible SVB the beat was classified as ventricular

The ECG material was analysed by the two computer programs and the results were presented on a 3-channel mingograph The tracings showed the ECG the arrhythmia diagnosis (alarm) in alphanumeric printing and a special classification code This coding made it possible in most cases to determine the probable reasons for incorrect classification with the two programs The performance of either program in some ventricular arrhythmias was also studied These included VF or VT (VT four or more consecutive VBs with a rate >120/min) two three or more than three VBs in succession ventricular bigeminy and more than 5 VBs/min The automated analysis was only performed once and no changes in the computer program or principles for manual interpretation were made during the study

Usually the staff was unaware of the ECG recordings which were made in a separate room No particular instructions were given regarding a preferable configuration of the complexes or the maximal noise-level that could be accepted Therefore some recordings were relatively rich in artefacts and two original ECG recordings had to be omitted one due to an unfavourable beat configuration (pointed P and T waves in combination with a low QRS amplitude) and one due to frequent noise making a proper manual interpretation impossible

Results About 50 000 ECG complexes were analysed in each patient The total number of VBs was 2 775 and out of these 48 and 60% were detected by Program I and II respectively The detection rate in indi idual patients with Program I and II ranged from 0 to 85% and from 35 to 95% respectively Abnormal non-VBs were rarely interpreted as VBs with either program Out of the ordinary complexes 0 06 and 0 02% were falsely classified as VBs with Program I and II respectively Artefacts gave rise to false positive VB detections corresponding to 0 15 and 0 04% of the total number of complexes respectiv ly The number of correctly detected VB

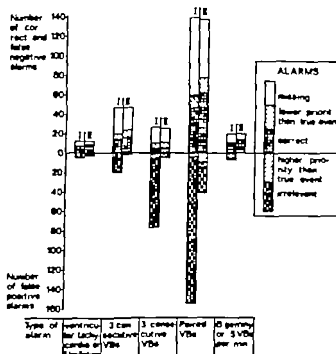


Fig. 10 Correct false positive and false negative alarms with Program I and II respectively studied with taped ECG from 12 patients

about 25% higher and false VB detection only 1/3 with Program II as compared to Program I However statistical analysis (sign test Documenta Geigy 1962) did not reveal any significant difference in performance between the two programs regarding false positive or false negative VB detection

About 50% of some ventricular arrhythmias were detected with a slightly higher figure with Program II compared to Program I (Fig 10) However the number of irrelevant alarms (artefacts being falsely interpreted as VBs) was more than 6 times greater with Program I than with Program II This resulted in a correct irrelevant alarm ratio corresponding to 1 3 and 3:1 with Program I and II respectively

Table VI Pr bable reasons for misclassifications of VBs with Program I and II (%)

	Program I n=1452	Program II n=1095
Inhibition of the analysis due to artefacts	3	16
Inhibition due to high derivativ of VB	1	
R wave und tected due to a low amplitude	5	4
Prematurity/compens tory paus abs nt	17	8
Narrow QRS/low orr lation with prototype VB	63	
Classified s normal beat	10	4
Classified as aberrant SVB		10
Failu e of parameterization		22
VB followed by und fined complex		3
New wavef rm		33
Other r unknown	1	
	100	100

Comments. With Program II arrhythmia analysis was blocked at a lower noise level compared to Program I Signal noise resulted in a higher proportion of missed VBs with Program II (Table VI) A majority of undetected VBs however were accompanied by a monitoring status alarm and in all these except faulty electrode contact all abnormal waveform groups were deleted automatically As the first and sometimes also the second complex in a waveform group was unreported a high level of noise could also influence the performance in noise free portions of the ECG Signal artefacts also increased the risks for failure of the parameterization procedure

Abnormal groups were deleted (Program II) if no new complexes were added within a certain period of time As the first single complex in a new group was ignored patients with a low VB frequency also showed lower figures for correct VB detection In patients with more than 1 VB/10 min and excluding one patient with a very high noise-level 84%

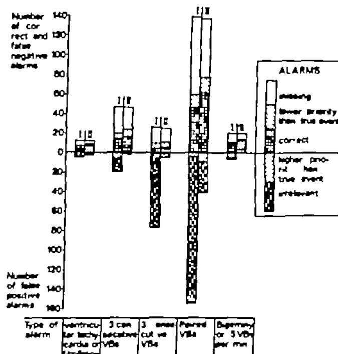


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Table VI Probable reasons for misclassifications of VBs with Program I and II (%)

	Program I n=1452	Program II n=1095
Inhibition of the analysis due to artefacts	3	16
Inhibition due to high derivative of VB	1	
R wave undetected due to a low amplitude		4
Prematurity/compensatory pause absent	17	8
Narrow QRS/low correlation with prototype VB	63	
Classified as normal beat	10	4
Classified as aberrant SVB		10
Failure of parameterization		22
VB followed by undefined complex		3
New waveform		33
Other unknown	1	
	100	100

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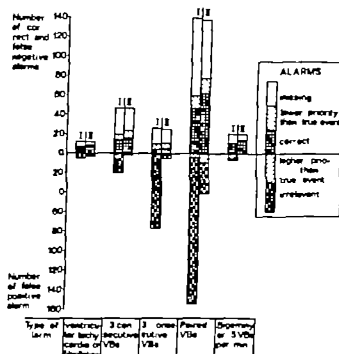


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punched out on paper tape which was used to summarize the results of the computer analysis The alarm write-outs were used to establish a direct relationship between alarms and arrhythmias The following abnormal beat categories were identified in the manual classification premature VB (PVB) possible VB and SVB This separation was based on prematurity QRST aberrancy and an increase in the QRS interval A deviation from normal in all three respects was set up as a requirement for a PVB A deviation from normal in two resulted in a possible VB diagnosis However narrow premature and sightly aberrant beats were classified as SVBs as well as beats of intermittent BBB type When possible P wave information was also considered The SVB group comprised abnormal beats not fulfilling the criteria for PVBs or possible VBs Ordinary complexes but not abnormal ones distorted by artefacts were classified as artefacts In the evaluation of the monitoring system the manual interpretation was used as a reference and the PVB and possible VB groups were combined to a single VB category The highest priority alarm that should be present at ideal performance of the system was determined for each minute of monitoring The actual alarms were compared to expected outcome at ideal performance The result of this comparison was summarized in terms of total time for correct (C) alarms lower (L) or higher (H) priority than expected alarms missed or undetected (U) alarms irrelevant (I) alarms and monitoring status alarms (A) possibly suppressing the detection of a true arrhythmia episode The total time of each of the above categories was calculated for all arrhythmias studied with reference except for I alarms to the expected alarm and not to the actual alarm The monitoring status alarms were only studied when these alarms possibly suppressed the detection of a true alarm Even if a single alarm was reset in a shorter time 4 min were always added to the total If an alarm lasting for several minutes was reset earlier than expected the time remaining to correct alarm reset was regarded as U For U alarms a 4 min reset time was counted H alarms were noted only when the reported alarm had been elicited by the true alarm event otherwise one I and one U al rm were marked An L alarm was noted only if the given alarm could be related to the real ECG event in other cases a U larm was recorded I alarms with a lower priority than the highest priority alarm were ignored A C alarm was not noted in U A or L situations even if the reported alarm in itself was correct The alarm more than 5 SVBs/min when undetected was marked as L if the

Table VII Effect of VB frequency on automated arrhythmia classification Program I=I, Program II=II

Average VB frequency	No of recordings	True no of VBs	Correctly detected VBs			
			Total material (%)		Mean of individual %-values	
			I	II	I	II
More than 1 VB/10 min	5	1226	61	83	56	84
Less than 1 VB/10 min	6	228	34	44	35	44

of all VBs were correctly classified (Table VII) This figure must be regarded as satisfactory in view of the principles for data collection However, even Program I performed better in patients with more frequent ventricular arrhythmias but the difference was smaller (Table VII) A more efficient suppression of artefacts in Program II was obtained partly at the price of a lower VB detection rate in patients with a low frequency of ventricular arrhythmias

EVALUATION OF ARRHYTHMIA ALARMS FROM A MONITORING SYSTEM BASED ON PROGRAM II

Program II was implemented into an 8-patient monitoring system The system was taken into routine use in 1976 and in August the same year the alarm function for all but the "R-on-T VBs and the missed QRS alarms was evaluated The former alarm could not be studied due to difficulties in obtaining an accurate manual interpretation the latter owing to an error in the computer program

A continuous ECG recorded from all patients at a speed of 10 mm/s and analysed by the author without knowledge of the result from the computer monitoring made it possible to estimate the true incidence of arrhythmias All alarms produced by the monitoring system were

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rhythm at the nearest 10 min print-out was marked as irregular The alarm function in tachycardia bradycardia and multiform VBs was only studied when such an alarm was produced by the system Standard rate limits for the definition of various arrhythmias were used (cf Table II) The alarm limits for bradycardia and tachycardia were modified whenever there was a definite change in HR outside preset limits VB detection was inhibited at all monitoring status alarms except "faulty electrode contact" Alarms were not studied when the continuous ECG recording was interrupted

Results Fifty-five patients were monitored during ten 24-hour periods for a total of 1 009 h However about 10 h of monitoring was not available for interpretation due to short breaks in the ECG recordings Average monitoring time in each patient was 18 0 h (0 2 - 24 0 h) A total of 5 million ECG complexes were analysed Five of the studied alarms (asystole VF VT more than 3 consecutive VBs and extreme bradycardia) occurred rarely and thus the performance in these conditions could not be properly analysed No case with idioventricular rhythm fulfilling the definition used in the computer program was documented during the period of study One patient with total block and an external pacemaker had short interruptions of pacemaker rhythm due to triggering problems which resulted in alarms for "more than 3 consecutive VBs" but these alarms were not otherwise considered

Alarms for 2 or 3 consecutive VBs ventricular bigeminy and SVT were correctly reported in 45% of expected alarm time at optimal performance (Fig 11) I alarms amounted to about 20% of the total alarm time in these conditions but I alarms for ventricular bigeminy or SVT were rare The performance among the lowest priority *arrhythmias* was better (Fig 12) about 3/4 of alarm time was correctly indicated A majority of L and U alarms resulted from misclassification of possible VBs Total L and U alarm time was reduced by a factor of 0 7 if possible VBs" were regarded as true SVBs when not interpreted as VBs by the computer

Total expected alarm time (C + L + H + U + A) in top middle and low priority arrhythmias was 0 7 34 3 and 98 6 h respectively Thus the total alarm time for arrhythmias was 134 h *for 70% of this time* a C alarm was present for 13%

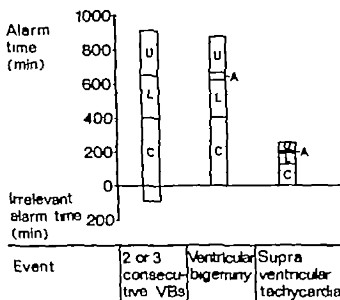


Fig. 11 Monitoring system performance in some arrhythmias in the second priority level C correct diagnosis U=missed or undetected event L=lower priority than correct (even if within correct priority level) A=monitoring status alarm present

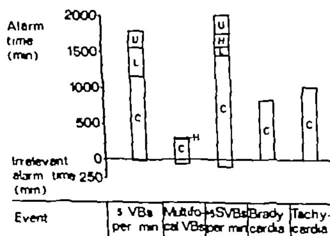


Fig. 12 Monitoring system performance for arrhythmias in the lowest priority level H higher priority than correct (even if within the same priority level) Other symbols as in Fig 11

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Results Fifty-five patients were monitored during ten 24-hour periods for a total of 1 009 h However about 10 h of monitoring was not available for interpretation due to short breaks in the ECG recordings Average monitoring time in each patient was 18 0 h (0 2 - 24 0 h) A total of 5 million ECG complexes were analysed Five of the studied alarms (asystole VF VT more than 3 consecutive VBs and extreme bradycardia) occurred rarely and thus the performance in these conditions could not be properly analysed No case with idioventricular rhythm fulfilling the definition used in the computer program was documented during the period of study One patient with total block and an external pacemaker had short interruptions of pacemaker rhythm due to triggering problems which resulted in alarms for "more than 3 consecutive VBs" but these alarms were not otherwise considered

Alarms for 2 or 3 consecutive VBs ventricular bigeminy and SVT were correctly reported in 45% of expected alarm time at optimal performance (Fig 11) I alarms amounted to about 20% of the total alarm time in these conditions but I alarms for ventricular bigeminy or SVT were rare The performance among the lowest priority arrhythmias was better (Fig 12) about 3/4 of alarm time was correctly indicated A majority of L and U alarms resulted from misclassification of possible VBs Total L and U alarm time was reduced by a factor of 0 7 if possible VBs were regarded as true SVBs when not interpreted as VBs by the computer

Total expected alarm time (C + L + H + U + A) in top middle and low priority arrhythmias was 0 7 34 3 and 98 6 h respectively Thus the total alarm time for arrhythmias was 134 h for 70% of this time a C alarm was present for 13%

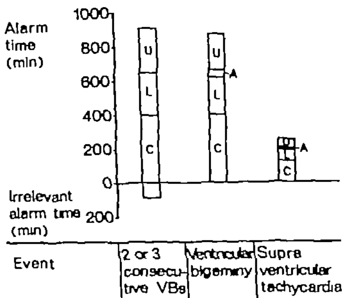


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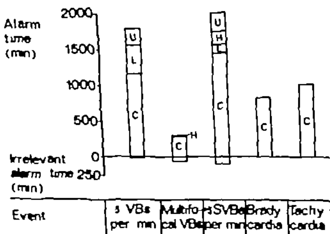


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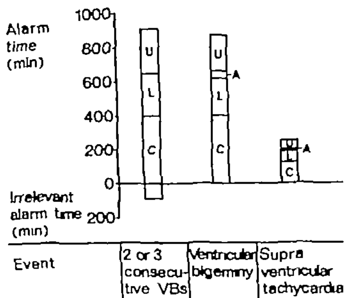


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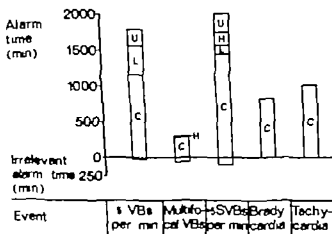


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PERFORMANCE OF THE MONITORING SYSTEM IN ASYSTOLE VENTRICULAR FIBRILLATION AND VENTRICULAR TACHYCARDIA

In the 10-day evaluation study described in the preceding section only a few highest priority arrhythmias occurred during the period of investigation Therefore alarm function in asystole VF and VT was investigated during 4 weeks of routine monitoring using a continuous ECG from all patients as a reference Only the first 10 episodes of the above arrhythmias in each patient were studied This reference ECG also contained a computer generated alphanumeric time marking which facilitated the comparison between the alarm write-outs and the manual interpretation Thus ECG examination was performed without knowledge of the computer analysis and essentially the same criteria for the classification of heart beats were practised as in the 10-day study However questionable abnormal beats were coded as SVBs rather than VBs

Results: Sixty five patients were monitored for a total of 3 400 h The monitoring system performance in the highest priority arrhythmias is summarized in Fig 13

In 5 patients a total of 24 asystole episodes were detected manually Eight of these were accompanied by a correct alarm and two remained undetected by the automated system

Table VIII Accuracy of arrhythmia incidence as estimated from alarm write-outs

Arrhythmia	No of patients with				Arrhythmia on write-out (%)
	verified arrhythmias	correct alarms	incorrect alarms only	missing alarms only	
2 or 3 consecutive VBs	25	16	2	7	72
Ventricular bigeminy	11	9	1	1	91
SVT	14	13	1		100
More than 5 VBs/min	18	16		2	89
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(mean)					(89)
VT	19	11	4	4	79

an L alarm for 3% an H alarm for 13% a C alarm and for 0 7% of the total time the arrhythmia occurred simultaneously with a monitoring status alarm with a higher priority The total number of I alarms was 87 compared to 732 for C alarms An I alarm was present for 6 1 h Monitoring status alarms were present for about 40 h The alarm change electrode placement" constituted more than 50% of this time

By studying the performance of the monitoring system in individual patients it was possible to assess the usefulness of the monitoring system for estimation of arrhythmia incidence in a large material of CCU patients About 90% of the patients with various ventricular and supraventricular arrhythmias were detected by the automated system (Table VIII) In a small number of patients certain arrhythmias were completely missed or incorrectly reported

Comments. The performance of the system in multiform VBs tachy- and bradycardia was not studied in exactly the same way as the other alarms since L and H alarm time for these former conditions was not counted It is supposed that L and H alarm time for the HR alarms was negligible Possibly monitoring status alarms blocked some tachy-/bradycardia alarms

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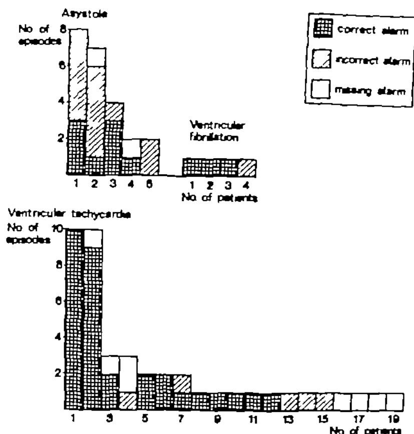


Fig. 13 Monitoring system performance in individual patients with reference to asystole VF and VT

Four VF episodes in 4 patients were found The computer diagnosis was VF in three and VT in one patient

Thirty-one out of 44 runs of VT were correctly detected by the monitoring system Eight VT episodes were undetected Two of these were preceded by artefacts which probably inhibited arrhythmia analysis Another two were unrecognized due to inhibition of VB detection on account of an unfavourable shape of the ordinary ECG complexes On three occasions VT was undiscovered for unknown reasons

Time delay from the last QRS to the alarm in true asystole was less than 15 s except on two occasions when artefacts inhibited the alar

and check electrodes was reported after 40 and 60 s The undetected asystole episodes had been preceded by alarms for VF and extreme bradycardia Arrhythmia alarm delay in VF and in detected runs of VT ranged from 5 to 14 s and from 2 to 5 s respectively

During the 4-week period 9 false positive asystole alarms were generated Six of these occurred when a bedside monitor had been disconnected from the wall connector without a previous stand-by operation The rest were caused by electrode problems and had been preceded by the message check electrodes The number of false positive VF and VT episodes was 13 in 3 patients and 38 in 2 patients respectively One patient contributed 37 false positive VT alarms

Comments: The 4 week period was not sufficiently long for a proper evaluation of the VF alarms since only 4 episodes occurred during the time period In all these cases however a highest priority alarm was reported indicating a high sensitivity of the system to VF The relatively high number of misclassifications in true asystole were due either to small baseline shifts or to marked P waves in relation to the QRS in a few patients with total block The asystole alarm was suppressed when the power of the signal exceeded a relatively low level Therefore following this investigation threshold values in the computer program were modified in order to increase the specificity of the system to asystole False positive asystole alarms were few and should be possible to reduce further by bedside equipment measuring the electrode impedance

The number of false positive VT alarms was relatively high in one patient with rapid atrial fibrillation and BBB Modifications in the program to decrease the number of false VF alarms have been suggested (Nygårds & Hulting 1977)

With the method used for studying the performance allowing only the first 10 episodes in each patient to be included the results will be influenced by differences in performance between patients with a small or a large number of arrhythmias In the present investigation 53% of the first VT episodes in each patient were correctly classified It could be calculated that about 90% of all VT episodes were correctly detected since the performance was better in patients with frequent runs of VT

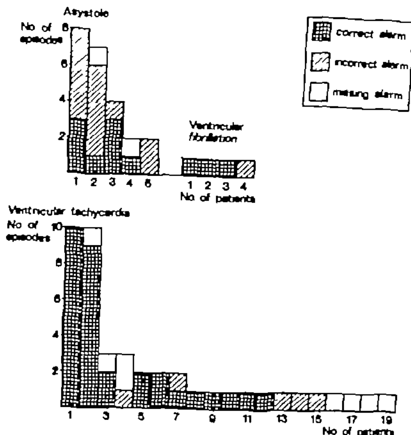


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VBs and non-VBs partly rested on the difference of QRS width between a reference complex and each new waveform It is supposed that this difference on the average was less in patients with atrial fibrillation and/or BBB

In the first two evaluations (I and II) false positive VB detection due either to misclassification of normal beats or noise with Program I was about the same even though the amount of noise differed in the two ECG materials The extension of artefact inhibition time from 2 to 4 s might explain the above observation VB detection rate with Program I declined markedly in the second study There were probably several reasons for this The diagnostic criteria used in the manual interpretation were possibly changed in such a way that some types of beats which were labelled abnormal non-VBs in the first study (I) were classified as VBs in the second study (II) This explanation might partly account for the lower rate of false positive detections (abnormal non-VBs) with Program I in the second as compared to the first evaluation study The performance of the system in the possible VB group was markedly better with Program II than with Program I However the factors of importance for missed VB detection with Program I were about equally distributed in the first two studies Also irregular rhythm was more common in 15 patients rich in ventricular arrhythmias (I) than in patients with AMI (II) The difference in performance found in comprehensive evaluations of essentially the same arrhythmia detector indicates that the performance of the monitor is markedly influenced by the ECG material It is possible that the selection of patients with AMI and a relatively short admission delay resulted in a higher than average percentage of difficult ECG records both from the point of beat shapes and signal artefacts In the 10-d y evaluation study (III) all patients admitted to the CCU were included and the start of monitoring and the length of CCU stay in each patient were not influenced by the investigation The selection of patients in the last evaluation (IV) was also unbiased In this part of the study AMI was diagnosed in 25 patients and VT was detected in the write-outs in 8 of these giving a VT incidence of 32% in AMI compared to 39% during a 12-month period (VI) This indicates that other possibly important factors for system performance such as electrode care were not affected by the investigation Also the ratio of correct to incorrect VT alarms during the 8 week and a 5-month period of

One patient with rapid atrial fibrillation and intermittent aberration contributed 36 of 37 false positive VT alarms There does not seem to be any easy way to reduce the number of false VT alarms in such patients In a majority of patients with atrial fibrillation and/or conduction defects no false positive VT or VF alarms were reported

All patients with asystole or VF had at least one of these arrhythmias reproduced on the alarm write-outs as shown in Fig 13 Fifteen out of 19 patients with true VT could be recognized after scrutiny of the alarm write-outs However VT was detected by the computer in another 3 patients in two the continuous ECG was interrupted and in one patient VT was overlooked in the manual analysis In 6 cases of missed VT detection the length of the arrhythmia episode was only 4 beats Thus 3/4 of undiscovered VT episodes had the minimum length (4 beats) contrasting to 1/4 of correct VT detections This indicates that the performance of the system was better in longer runs of VT As most runs of VT were longer than 4 beats a more stringent definition of this alarm would probably have given a better monitoring system performance in this arrhythmia

DISCUSSION

The distinction between ventricular and supraventricular beats may be difficult or even impossible from a single lead recording of the ECG This depends on a relatively common inconstancy or absence of P waves in the bipolar ECG and on difficulties in determining the true QRS axis and QRS configuration e g a BBB pattern Also multiple lead ECGs are usually recorded at a higher speed which gives a better resolution and a more accurate time interval estimation e g QRS width The difficulties of interpretation will result in a certain variability between different interpreters as manifested in the first study (I) Thus divergent opinions whether to refer a complex to the VB/probable VB group or not was seen in about 8% of all abnormal beats In patients with atrial fibrillation the same figure was obtained However the automated analysis was less accurate in this arrhythmia since rhythm criteria could not be used in irregular rhythm Also the arrhythmia analysis in atrial fibrillation was also complicated by a greater number of abnormal waveform groups and a longer average QRS interval In Program II the distinction between

REVIEW OF REPORTED EVALUATIONS OF OTHER ARRHYTHMIA DETECTORS AND MONITORING SYSTEMS

As stated earlier relatively few evaluations of other arrhythmia monitors have been presented Only a few previous beat-by-beat studies comprise more than 100 000 beats The proportion of patients with atrial fibrillation has usually been low or unreported Most studies presented below are comparable to the first investigation (I) regarding the size of the ECG material and the principles for ECG data collection A comparison with the present long-term studies (III and IV) is hardly possible

Oliver et al (1971) using the Azteo-Argus algorithms and allowing adjustment of the signal amplification reported a VB detection rate of 78% False positive VBs constituted 0 4% out of a total of around 50 000 beats Yanowitz et al (1975) using the same principal algorithms but a simplified diagnostic scheme compared to that of the former authors reported correct detection of 90% out of 3 163 VBs and 25 false VB detections corresponding to 0 07% of all beats However to obtain a maximal performance some of the parameters in the program were optimized in each patient A third system based on the Aztec preprocessing algorithms has been reported by Harrison et al (1974) An average of 84% of all ventricular premature beats was correctly identified with a false positive rate of 0 14%

The accuracy of VB detection using a simple correlation technique was described in an early study by Feldman et al (1971) The material contained 48 000 beats but only 141 VBs 100 of which were correctly classified Twenty-two false positive VB detections were made However only 4 out of 16 patients in the study had a significant arrhythmia An arrhythmia detector based on the correlation technique and also on the grouping of similarly shaped beats was developed and evaluated by Shah et al (1977) The system allowed for recognition of low amplitude complexes performing an automated backward search for ectopic beats when a prolonged R-R interval was discovered The test material comprised 146 635 beats 5 729 labelled as ventricular and was obtained from 57 half hour records from 30 patients The recordings were selected by a trained cardiology technician Off-line testing showed a correct VB classification rate of 95% In 2 patients with atrial fibrillation the corresponding figure was 93% False

monitoring was about the same (IV)

In the two beat-by-beat evaluations (II and III) questionable beats were diagnosed as VBs rather than SVBs At uncertain interpretation regarding some defined arrhythmias these were classified as supraventricular rather than ventricular (IV and VI) This change in diagnostic policy during the study could have resulted in an improved performance of VT but since questionable arrhythmias were relatively rare (cf VI) the overall effect of the above measure was probably small

The manual cancelling of VB monitoring affects the monitoring system performance During the 4-week period such an action was undertaken on two occasions but did not however, influence the results (IV) During a 4-month period (February - May 1978) inactivation of VB recognition which left the HR and power spectrum dependent alarms unaffected took place in 9 cases out of a total around 300 in 5 patients intermittent pacemaker rhythm resulted in frequent false alarms for VBs in succession in 2 patients frequent false VT alarms were seen due to an intermittent rate-dependent aberration in one patient very frequent true VT alarms annoying the staff were observed and in another patient the nurses were much disturbed by frequent "what has happened? alarms During the abovementioned 4-month period 2 patients were not immediately accepted for monitoring due to a slow multifocal rhythm In these 2 patients the manual definition of the "normal" beat was almost impossible Thus significant monitoring problems were present in about 3% of the patients

It was obvious that the monitoring system performance as expressed in the ratio of correct to irrelevant alarms was dependent on the alarm reset time (III) As the irrelevant alarms were usually shorter an extension of the alarm reset time would decrease the above ratio i e the apparent performance would deteriorate

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Hultgren et al (1975) reported the results from an evaluation study encompassing 188 276 beats The manual classification however was not blinded and VBs and other abnormal or premature beats were not separated In summary, 98% of all abnormal beats were detected by the system with a false positive rate of 0 10% Quinn et al (1975) evaluated an arrhythmia detector with 15 min records from 20 patients Eighty-six per cent of 2 021 VBs were recognized The false positives comprised 0 31%

A digital arrhythmia detector permitting individual control of parameter settings was developed and evaluated by Bussman et al (1975) In a material of 108 000 beats with nearly 10 000 VBs 96% of the VBs and 99% of the SVBs were correctly detected

Except for the present study only two reports concerning the performance of the alarm function during prolonged monitoring have been published so far Vetter & Julian (1975) studied the alarms from a hybrid arrhythmia detector in 32 CCU patients AMI was diagnosed in 22 cases The average monitoring time on the computer in each patient was 34 h The arrhythmia detector correctly recognized all 85 episodes of ventricular tachycardia The true arrhythmia incidence however was obtained with the aid of the arrhythmia detector For this purpose taped ECG material was fed into the computer and the parameter settings of the detector were modified to increase the sensitivity of the arrhythmia analysis The prevalence of VT exceeded that of paired VBs frequent VBs and tachy- or bradycardia This could possibly be explained by special criteria for the definition of various arrhythmias No specific arrhythmia diagnosis was delivered but a three-level graded sound accompanied each alarm The total number of false positive alarms during 1 081 h of monitoring was more

In a recent study by Frost et al (1977) a computerized arrhythmia alarm system was tested during 200 hours of monitoring The number of patients and the length of monitoring in each patient were not specified An analog HR alarm system operated in parallel with the computer system Using a relatively simple set of arrhythmia diagnoses and including monitoring status alarms true alarms constituted 53 and 8% of computer-generated and analog alarms respectively The ECG was reproduced only at an alarm and thus the number of undetected arrhythmias could not be determined Concerning VT defined as 5 or more VBs in succession with a rate above 99 one true and 8 false positive computer alarms were reported

E aluation results from a 2 lead monitoring system in 306 patients showed correct detection of 91% of VBs (total 3 051) and 86% of SVBs (total 1 752) In atrial fibrillation 69% of VBs were correctly diagnosed (Bernard et al 1977)

positive VB detection was 0 10% Paired VBs occurred on 131 occasions 81% correctly identified The performance in VT (not defined) was regarded as satisfactory with correct detection of 87% of VBs belonging to this arrhythmia Two false negative and 3 false positive VT detections were observed The results obtained by Shah et al were better than those reported by most earlier investigators but surprisingly aberrant non-VBs were absent in the ECG material

Hultgren et al (1975) reported the results from an evaluation study encompassing 188 276 beats The manual classification however was not blinded and VBs and other abnormal or premature beats were not separated In summary 98% of all abnormal beats were detected by the system with a false positive rate of 0 10% Quinn et al (1975) evaluated an arrhythmia detector with 15 min records from 20 patients Eighty-six per cent of 2 021 VBs were recognized The false positives comprised 0 31%

A digital arrhythmia detector permitting individual control of parameter settings was developed and evaluated by Bussman et al (1975) In a material of 108 000 beats with nearly 10 000 VBs 96% of the VBs and 99% of the SVBs were correctly detected

Except for the present study only two reports concerning the performance of the alarm function during prolonged monitoring have been published so far Vetter & Julian (1975) studied the alarms from a hybrid arrhythmia detector in 32 CCU patients AMI was diagnosed in 22 cases The average monitoring time on the computer in each patient was 34 h The arrhythmia detector correctly recognized all 85 episodes of ventricular tachycardia The true arrhythmia incidence however was obtained with the aid of the arrhythmia detector For this purpose taped ECG material was fed into the computer and the parameter settings of the detector were modified to increase the sensitivity of the arrhythmia analysis The prevalence of VT exceeded that of paired VBs frequent VBs and tachy- or bradycardia This could possibly be explained by special criteria for the definition of various arrhythmias No specific arrhythmia diagnosis was delivered but a three-level graded sound accompanied each alarm The total number of false positive alarms during 1 081 h of monitoring was more than 300

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Table IX Definition and ranking of arrhythmias in the manual interpretation of alarm write-outs

Ranking	Arrhythmia	Criteria
1	Asystole	R R interval >5 0 s
2	VF	Rapid oscillating irregular rhythm with a duration >5 0 s
3	VT	4 or more consecutive VBs with a rate >1 0/min
4	Run of VBs	3 consecutive VBs with a rate >50/min or 4 or more VBs in succession with a rate 51-120/min
5	Extreme bradycardia	HR <35/min
6	Paired VBs	
7	R-on-T VBs	This arrhythmia was only studied when the corresponding alarm had been delivered
8	Ventricular bigeminy	3 or more VBs alternating with normal beats - at least 2 of the VBs should be visible on the write-out
9	SVT	4 or more SVBs with a rate >120/min - this diagnosis required SR prior to or after the arrhythmia episode
10	More than 5 VBs/min	Alarm write-out triggered by a VB
11	More than 5 SVBs/min	Alarm write-out triggered by SVB
12	Tachycardia	SR or supraventricular rhythm with a QRS rate >120/min
13	Bradycardia	SR or supraventricular rhythm with a QRS rate <50/min

if the expected number in the four field table was 5 or less The term significant as used below refers to a probability p<0 05 (Reference: Bailey, N Statistical methods in biology 1961)

Results: The investigation comprised 339 patients with proven AMI and 340 patients without proven AMI

ARRHYTHMIAS DETECTED WITH THE PRESENT MONITORING SYSTEM DURING LONG-TERM USE

The following investigation was undertaken in order to analyse arrhythmia incidence in the CCU and to investigate the prognostic importance of various arrhythmias

During 12 months 669 patients were admitted to the CCU because of a suspected myocardial infarction (MI) and monitored on the computer system (VI) Another 10 monitored patients who were admitted for other reasons but later proved to suffer from AMI were also included in the patient material However patients with an uncertain or a long (>96 h) time delay between onset of symptoms and start of monitoring were excluded The CCU did not receive all cardiac patients in the hospital admitted for ECG monitoring during the 12-month period A total of 86 cardiac patients were observed in a nearby intensive care unit (ICU) Reasons for ICU admission were (1) coma persisting after resuscitation (2) imminent or overt respiratory failure and (3) all beds with automated monitoring occupied

All write-outs produced by the monitoring system during 12 months were collected and analysed An arrhythmia diagnosis was usually made without consideration of the diagnostic message given by the computer However the definition and ranking of arrhythmias were essentially the same as those adopted in the computer program (Table IX) When two or more arrhythmias were present on the write-out the highest ranked condition was chosen The HR in ordinary supraventricular or ventricular rhythms was obtained manually The same diagnostic criteria for distinguishing between VBs and SVBs were used as described in the 4-week study (cf pp 39 and 43) In each patient the length and rate of all episodes of VT were noted

Lidocaine was usually withheld until VT or VF had been diagnosed and was given as a bolus followed by a continuous infusion for at least 12 h at a rate of 1 - 3 mg/min

The Chi-square test (four field table two-tailed test) with Yates correction was used for the evaluation of statistical significances in relative numbers at the 5 1 and 0 1% level The exact test was used

Table IX Definition and ranking of arrhythmias in the manual interpretation of alarm write-outs

Ranking	Arrhythmia	Criteria
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6	Paired VBs	
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9	SVT	4 or more SVBs with a rate >120/min - this diagnosi requir d SR prior t or after the arrhythmia episode
10	More than 5 VBs/min	Al rm write-out trigge ed by a VB
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12	Tachycardia	SR or supravent icula hythm with a QRS rate >120/min
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The following investigation was undertaken in order to analyse arrhythmia incidence in the CCU and to investigate the prognostic importance of various arrhythmias

During 12 months 669 patients were admitted to the CCU because of a suspected myocardial infarction (MI) and monitored on the computer system (VI) Another 10 monitored patients who were admitted for other reasons but later proved to suffer from AMI were also included in the patient material However patients with an uncertain or a long (>96 h) time delay between onset of symptoms and start of monitoring were excluded The CCU did not receive all cardiac patients in the hospital admitted for ECG monitoring during the 12-month period A total of 86 cardiac patients were observed in a nearby intensive care unit (ICU) Reasons for ICU admission were (1) coma persisting after resuscitation (2) imminent or overt respiratory failure and (3) all beds with automated monitoring occupied

All write-outs produced by the monitoring system during 12 months were collected and analysed An arrhythmia diagnosis was usually made without consideration of the diagnostic message given by the computer However the definition and ranking of arrhythmias were essentially the same as those adopted in the computer program (Table IX) When two or more arrhythmias were present on the write-out the highest ranked condition was chosen The HR in ordinary supraventricular or ventricular rhythms was obtained manually The same diagnostic criteria for distinguishing between VBs and SVBs were used as described in the 4-week study (cf pp 39 and 43) In each patient the length and rate of all episodes of VT were noted

Lidocaine was usually withheld until VT or VF had been diagnosed and was given as a bolus followed by a continuous infusion for at least 12 h at a rate of 1 - 3 mg/min

The Chi-square test (four field table two-tailed test) with Yates correction was used for the evaluation of statistical significances in relative numbers at the 5 1 and 0 1% level The exact test was used

T ble XI CCU mort lity in l tion to a hythmi inciden in 339 pati nt with proven AMI and in 340 patient without prove AMI s not ignifica t

	CCU mortality(%) in AMI			CCU mort lity(%) in nonp oven AMI			Diff renc be- tween AMI and non AMI p tients with arrhythmia
	with r hythmia	witho t arrhythmia	Diff ren e	with rrhythmia	without rrhythmia	Differ ce	
Asystole	83	11	p<0 001	83	1	p<0 001	n s
VF	45	14	p<0 01	50	2	n s	n s
VT	20	13	n	9	1	n s	n s
Run of VB	14	18	n s	2	2	n s	n s
Extreme bradycardia	61	11	p<0 001	5	2	n s	p<0 001
Paired VBs	13	23	p<0 05	3	2	n s	p<0 01
R-on-T VBs	8	17	n s	0	3	n s	n s
V ntri lar bigeminy	13	17	n	0	3	n s	p<0 01
SVT	10	22	p<0 01	1	3	n s	p<0 05
Mor than 5 VBs/min	18	14	n s	1	3	n s	p<0 001
Mor than 5 SVBs/min	16	16	n s	3	2	n s	p<0 01
Br dycardia	16	16	n s	4	1	n s	p<0 01
Tachycardia	20	11	p<0 05	6	0	p<0 01	p<0 01

Table X Arrhythmia incidence (%) in 339 patients with proven AMI and in 340 patients without proven AMI n s = not significant

	AMI	Non-AMI	Difference
Asystole	7	2	p<0 01
VF	6	2	p<0 05
VT	38	10	p<0 001
Run of VBs	50	17	p<0 001
Extreme bradycardia	11	6	n s
Paired VBs	72	38	p 0 001
R-on-T VBs	15	7	p<0 01
Ventricular bigeminy	31	20	p<0 01
SVT	50	22	p<0 001
More than 5 VBs/min	49	29	p<0 001
More than 5 SVBs/min	45	28	p<0 001
Bradycardia	39	45	n s
Tachycardia	55	34	p<0 001

All studied arrhythmias except bradycardia were significantly more common in the AMI group (Table X) Exclusion of arrhythmias occuring during the last hour in the CCU did not change this pattern even though a substantial reduction of asystole events followed after this procedure

Overall CCU and total hospital mortality in AMI were 16 and 21% respectively in non-AMI patients corresponding figures were 2 and 6% respectively CCU mortality in the various arrhythmias is shown in Table XI There were no significant differences in mortality between AMI and non-AMI patients for the following arrhythmias asystole VF VT run of VBs and R-on-T VBs However the absolute mortality was higher in most arrhythmias in the AMI group When mortality was calculated after the exclusion of arrhythmias recorded in the last hour the prognosis for patients with ventricular bigeminy and SVT also turned out to be similar in the two groups In patients with AMI the following arrhythmias were associated with a significant increase in mortality asystole extreme bradycardia VF and

XI CCU mo t lity i l tio to r hythmi in id in 339 pati t with proven AMI nd i 340 patients w hout proven AMI n not ignific t

	CCU mo tality(%) in AMI			CCU mort lity(%) in n proven AMI			Differ n e between AMI and non AMI patients with arrhythmia
	with rrhythmia	without arrhythmia	Differ nc	with rrhythmi	without rrhythmia	Differenc	
Asystole	83	11	p<0 001	83	1	p<0 001	n s
VF	45	14	p<0 01	50	2	n s	n s
VT	20	13	n s	9	1	n s	n s
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Ventri ul r bigeminy	13	17	n s	0	3	n s	p<0 01
SVT	10	22	p<0 01	1	3	n s	p<0 05
More than 5 VBs/min	18	14	n s	1	3	n s	p<0 001
More than 5 SVBs/min	16	16	n	3	2	n s	p<0 01
Bradycardia	16	16	n s	4	1	n s	p<0 01
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tachycardia No prognostic conclusions regarding mortality in AMI could be made in the following arrhythmias VT run of VBs R-on-T VBs ventricular bigeminy more than 5 VBs/SVBs and bradycardia Patients with paired VBs and SVT had a significantly lower CCU mortality than those without these arrhythmias This last observation, however was not confirmed when the total hospital mortality in AMI patients with or without SVT and/or paired VBs was analysed For all other studied arrhythmias the same prognostic information as mentioned above was obtained when total hospital instead of CCU mortality was considered

In the non-AMI group two arrhythmias were associated with a significant increase in CCU mortality namely asystole and tachycardia The same applied to paired VBs when total hospital mortality was considered

The incidence of ventricular tachycardia in AMI with the use of different definitions of this arrhythmia and mortality related to arrhythmia incidence is presented in Table XII AMI patients with 8 or more VBs in succession at a rate >120/min had a poorer CCU and total hospital prognosis than those with no or other runs of VBs

Comments. Total monitoring time for all 679 patients was 38 000 h Arrhythmias in such a large material could hardly have been analysed in a continuous ECG or from a semi-automated analysis of taped ECGs

The incidence of cardiac arrhythmias in AMI during CCU stay has been reported in a great number of publications (Spann et al 1964, Julian et al 1964 Meltzer & Kitchell 1966 Restieaux et al 1967 Lawrie et al 1967 Stock et al 1967 Lown et al 1967 Raftery et al 1969 Mogensen 1970 Henning & Lundman 1975) Patient selection definition of arrhythmias methods for arrhythmia documentation and principles for antiarrhythmic treatment have differed in the above studies and a comparison between the present investigation and earlier ones is difficult The restrictive use of lidocaine possibly contributed to a relatively high incidence of ventricular tachycardia However the incidence of paired VBs ventricular bigeminy frequent VBs/SVBs and tachy-/bradycardia certainly was higher than previously reported with conventional monitoring methods This indicates that the automated system worked efficiently The incidence of SVT found in the present

Table XII Incidenc of v ntricular tachycardia and runs of VBs in 339 patients with AMI and CCU mortality related to arrhythmia incidence n s = not significant

Criteria for ventricular tachyarrhythmia			CCU mortality (%)		
Minimum length (beats)	Rate above (min^{-1})	Incidence (%)	w th arrhythmia	without arrhythmia	Differen e
3	50	65	16	17	n s
3	100	57	16	16	n s
4	120	38	20	13	n
4	150	23	27	13	p<0 01
4	180	12	40	12	p<0 001
4	210	6	47	14	p<0 001
6	120	23	23	14	n
8	1 0	17	30	13	p<0 01
10	1 0	13	38	13	p<0 001
20	120	9	47	13	p<0 001
40	120	6	62	13	p<0 001

investigation was considerably higher than the figures between 2 and 11% previously reported (Julian et al 1964 Meltzer & Kitchell 1966 Lawrie et al 1967 Jewitt et al 1967 Lown et al 1967 Mogensen 1970) but different definitions could have partly contributed to this discrepancy

Regarding patients with nonproven infarctions arrhythmia incidence in a material of comparable size has not been reported earlier

As to the prognostic implications of various arrhythmias VT was not associated with a significantly increased mortality in AMI This observation contrasts to earlier reports (Lawrie et al 1967 Stock et al 1967 Dalle et al 1968 Raftery et al 1969 Mogensen 1970 Renning & Lundman 1975) It is possible that a high sensitivity of

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Criteria for ventricular tachyarrhythmia						
Minimum l ngth (be ts)	Rat above (min^{-1})	Incid nce (%)	CCU mortal ty (%) with arrhythmia	without arrhythmia	Difference
3	50	65	16	17	n s
3	100	57	16	16	n s
4	120	38	20	13	n
4	150	23	27	13	p<0 01
4	180	12	40	12	p<0 001
4	210	6	47	14	p<0 001
6	120	23	23	14	n
8	120	17	30	13	p<0 01
10	120	13	38	13	p<0 001
20	120	9	47	13	p<0 001
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of the automated monitoring system to VT resulted in the detection of a great number of relatively "benign" VT episodes Stricter criteria for the definition of ventricular tachycardia enabled us to discriminate more "malignant" arrhythmias (Table XII) Thus it is suggested that the definition of ventricular tachycardia in the computer program should be modified to include 6 VBs in succession with a rate >120/min

The high mortality in extreme bradycardia and a high number of immediate actions by the nurses in this arrhythmia motivates transferal of the corresponding alarm to the highest priority group

A heart rate above 100/min has been considered an indication of "pump failure" in AMI (Lown et al 1967) and the more restricted definition of tachycardia used in the computer program (HR>120/min) possibly contributed to the selection of severely diseased patients The poorer prognosis observed in AMI and non-AMI patients with tachycardia indicates that this alarm ought to be accompanied by an alerting signal and moved to the second priority level However in the latest version of the system an "extreme tachycardia" alarm (HR >150/min) has been added but neither the incidence of this alarm nor its prognostic value have yet been analysed In order to decrease the number of second priority alarms the benign character of paired VBs in AMI is sufficient evidence for assigning this alarm to the lowest priority level

INTERPRETATION TEST

All ECG interpretation in the 12-month investigation reported in the preceding section was done by the author and in a vast majority of the recordings only from analysis of alarm write-outs Therefore the possible differences in interpretation between the author and a reference group was studied This group was made up of 13 physicians Only three arrhythmias (alarms) were selected for this testing namely VF VT and SVT A comparison between the interpretation by this group and by the computer was also made

The write-outs were collected during one month (May 1977) chosen in advance by the author who collected the first probable or suspected episode of VF VT, and SVT from each patient as well as the first (probably) false alarm regarding the above arrhythmias Thus the test material included the first VF VT and SVT alarm from each patient Theoretically any patient could contribute 6 ECGs

Each physician received an atlas (photocopy) of 61 ECG strips and was asked to code each ECG with one of the following five alternatives and in the following order of priority: (1) VF (2) VT (3) SVT; (4) artefact and (5) other All records were analysed without clinical or other information on the patients The computer diagnosis had been concealed in the test material In the manual interpretation the same definitions of VF VT and SVT as given in Table IX were used The interpretation wa made individually and the test lasted for one hour maximally All participants were experienced in ECG interpretation and a majority had specialty competence in cardiology clinical physiology or internal medicine but only a few had experience from the monitoring system

Results: In Fig 14 16 the interpretation by the reference group by the author and by the computer is compared The ECG records were arranged to display an increasing number of positive diagnoses from left to right in the diagrams

VF diagnoses were made by the members of the reference group in 8 ECG records However only in three of the cases did a majority consider VF to be present and in no case did all members of the group consider to be the most likely diagnosis The computer system alone falsely

reported VF in one record with artefacts However no true episode of VF was included in the material and this conclusion was confirmed by comparison with clinical data afterwards

Regarding VT there was good agreement between the physicians and the author for most ECG records (Fig 15) In four instances (ECG nos 19 20 23 and 33 in Fig 15) a majority of the physicians and the author had divergent opinions ECG 19 showed a run of probably ventricular beats with a rate below 120/min, ECG 20 was considered questionable by the author and therefore referred to the SVT category ECG 23 showed SVT according to the author's opinion and ECG 33 showed a rapid regular rhythm with wide QRS complexes - a final diagnosis was made by the author after comparison with a diagnostic ECG which showed rapid supraventricular rhythm with a left BBB pattern

All records except one labelled SVT by a majority of the physicians were also classified as SVT by the author The exception ECG 27 in Fig 16, showed a run of only three SVBs according to the author s interpretation ECG 18 in Fig 16 and no 23 in Fig 15 were identical as were also several other records in Fig 14-16

Comments The selection of ECGs for the testing was to some extent dependent on the author s classification A number of missed and irrelevant SVT alarms were documented in the testing (Fig 16) but the principles used for ECG data collection did not permit an accurate evaluation of monitoring system performance from results in the interpretation test Only three arrhythmias were studied A comprehensive testing including all arrhythmias (alarms) reported by the system would require a great number of ECG strips Such a trial was not feasible from a practical point of view The difficulties in distinguishing VT and SVT were emphasized in the test Also the varying opinions regarding the most likely diagnosis of the same recording were apparent The principle for interpretation used by the author referring questionable arrhythmias to the supraventricular rather than to the ventricular category was responsible for discrepancy in interpretation in one write-out The same principle for classification was used in the 12-month study (VI) and possibly contributed rather to an underestimation of the true number of VT episodes The physicians inexperience in evaluating various artefacts in the write-outs was partly responsible for their incorrect

VF diagnoses

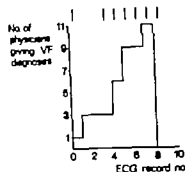


Fig. 14 Interpretation by 13 physicians by the author and by the monitoring system regarding VF A positive diagnosis by the computer is indicated by a short vertical line above the diagram No VF diagnosis was made by the author

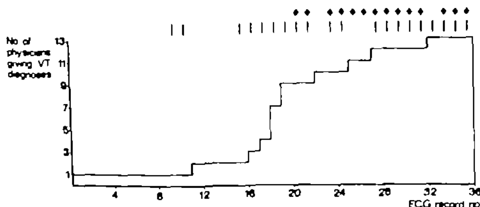
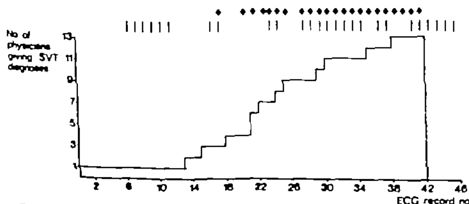


Fig. 15 Interpretation by the physicians by the author and by the monitoring system regarding VT A positive diagnosis by the author is indicated by a small square above the diagram other symbol as in Fig 14



16 Interpretation by the physicians by the author and by the ...ing system regarding SVT Symbols as in Fig 15

SOME OTHER ASPECTS OF AUTOMATED ARRHYTHMIA MONITORING WITH THE PRESENT SYSTEM

Placement of electrodes and desirable configuration of ECG complexes

The accuracy of ECG monitoring with Program II was influenced by the configuration of the QRST complex Thus the feature extraction procedure was compromised by small Q or S waves in the QRST complex Also a pointed positive or negative T wave in relation to the QRS was undesirable and often resulted in the alarm "change electrode placement The polarity of the signal however was irrelevant A schematic drawing in each patient room showed desired and unfavourable configurations of the ECG complexes (Fig 17) The monitoring status alarms seem to have been more helpful than the above drawing and usually guided the nurses to an acceptable beat shape

It is preferable to place the surface electrodes over the sternum since this position probably results in an ECG with less muscular noise compared with other thoracic lead positions Also with a sternal position of electrodes the ECG complex is less influenced by a change in position of the patient particularly turning to his left or right side

In all but a very low number of patients an acceptable beat configuration was obtained Low voltage in the ECG made it impossible to get an acceptable QRS amplitude in a few patients and resulted in relatively frequent false alarms for "bradycardia" and missed QRS but after a change in threshold values in the computer program these amplitude problems have diminished markedly A split QRS with a wide S wave sometimes observed in right BBB has been a nuisance in a few patients and resulted in repeated alarms for unfavourable electrode positions

The 12-lead diagnostic ECG contains information regarding the beat configuration expected from various placement of chest electrodes but the nurses have not utilized this information efficiently

Electrode artefacts could possibly be diminished by measures taken to reduce the stretching of the skin electrodes Also some regular

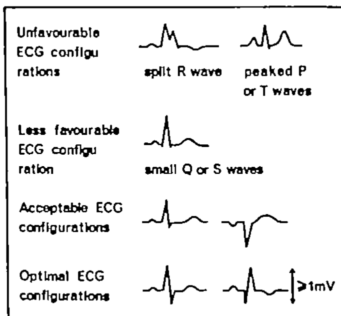


Fig. 17 Unfavourable acceptable and optimal configurations of ECG complexes (Diagram used in staff training)

testing of the electrode impedance would be advantageous but neither of these recommendations have been put into routine nor were they practised in any of the clinical evaluations previously described in this study

In summary an adequate QRS amplitude (1-2 mV) free from small Q or S waves should be sought Smooth P or T waves with amplitudes 1/3 or less of the QRS amplitude are desirable

SOME OTHER ASPECTS OF AUTOMATED ARRHYTHMIA MONITORING WITH THE PRESENT SYSTEM

Placement of electrodes and desirable configuration of ECG complexes

The accuracy of ECG monitoring with Program II was influenced by the configuration of the QRST complex Thus the feature extraction procedure was compromised by small Q or S waves in the QRST complex Also a pointed positive or negative T wave in relation to the QRS was undesirable and often resulted in the alarm "change electrode placement" The polarity of the signal however was irrelevant A schematic drawing in each patient room showed desired and unfavourable configurations of the ECG complexes (Fig 17) The monitoring status alarms seem to have been more helpful than the above drawing and usually guided the nurses to an acceptable beat shape

It is preferable to place the surface electrodes over the sternum since this position probably results in an ECG with less muscular noise compared with other thoracic lead positions Also with a sternal position of electrodes the ECG complex is less influenced by a change in position of the patient particularly turning to his left or right side

In all but a very low number of patients an acceptable beat configuration was obtained Low voltage in the ECG made it impossible to get an acceptable QRS amplitude in a few patients and resulted in relatively frequent false alarms for bradycardia and "missed QRS", but after a change in threshold values in the computer program these amplitude problems have diminished markedly A split QRS with a wide S wave sometimes observed in right BBB has been a nuisance in a few patients and resulted in repeated alarms for unfavourable electrode positions

The 12-lead diagnostic ECG contains information regarding the beat configuration expected from various placement of chest electrodes but the nurses have not utilized this information efficiently

Electrode artefacts could possibly be diminished by measures taken to reduce the stretching of the skin electrodes Also some regular

Other previously described methods for the reduction of false positive VF alarms should be implemented (Nygårds & Hulting 1977) A special procedure for the detection of low amplitude ectopic beats would be advantageous The ranking and priorities of some arrhythmia alarms should be changed in the way described on page 58 A special alarm should be given if the automated monitoring is interrupted

Education of personnel

All education regarding the handling of interactive procedures the use of monitoring on/off and alarm reset keys etc has been easy All new nurses were trained by their colleagues The time needed for an inexperienced person to learn how to operate the system and how to use the interactive programs has been less than half an hour in most cases The care of electrodes and their optimal placement however needs continuous attention and education from the staff physician

A schedule in the nurses station showed all the alarms and their priorities The codes of all interactive programs were listed on the video screen This information was not available in the patient rooms

ECG monitoring in patients with external pacemakers
and with other special rhythms

Intermittent external pacemaker activity has usually resulted in false alarms for VBs in succession A high frequency of such alarms has been annoying to the staff In these situations the VB detecting function has been turned off and the rate limits narrowed so that a dropped beat or the resumption of normal rhythm would be recognized from HR criteria only These actions usually worked satisfactorily A pacemaker rhythm overridden e g by SR with a narrow QRS complex resulted in the alarm new QRS after about 2 min The pacemaker pulse was usually undetected but on rare occasions it was sampled explaining a few alarms for check electrodes in pacemaker patients

The presence of continuous VT at the start of monitoring has usually been interpreted as tachycardia by the computer system Even for the human observer the distinction between VT on admission and a rapid rhythm with BBB is often impossible from the bipolar ECG In such

Starting monitoring

After the attachment of skin electrodes and the connection of patient cables to the bedside unit monitoring is started by pressing a special key on the unit After 15-45 s monitoring starts and HR will be indicated on the video screen If the ECG signal is unsatisfactory the message "check ECG signal" will be displayed

Monitoring for a selected patient may be initiated or terminated in any patient room or in the central station

Technical problems

The technical problems have been few after the introduction of the computerized monitoring system in clinical routine Overheating of the computer as a result of insufficient ventilation has occurred twice The keyboard of the video screen as well as the ink-jet pens of the Mingograph have been exchanged On a few occasions monitoring has stopped for unknown reasons In these cases the system has been restarted within seconds or minutes from the computer room by pressing a special key

Modifications in the computer program

All computer algorithms had been thoroughly tested before the system was taken into routine use in 1976 However since the introduction a few changes in the program have been necessary Some of these modifications have been mentioned earlier The lowest acceptable QRS amplitude was decreased from about 0 6 to 0 3 mV at the patient electrodes The asystole alarm was shown to be inhibited by moderate base line shifts or marked P waves and these findings made it necessary to change some threshold values The program has also been modified in order to accept patients with a very low HR - in the first version of the program 5 or more ECG complexes should be recorded within 10 s before a reference complex was approved The alarm extreme tachycardia" was added in 1977 Future improvements of the system should include a special subroutine for pacemaker patients and some circuits in the bedside equipment for measuring electrode impedance This last method would probably result in improved electrode care with a decrease in the number of irrelevant alarms

not cause any harm to the patients Lidocaine was given to 21% of 339 AMI patients VT and VF had been diagnosed in 70% and 24% of these patients respectively

In several patients without suspected AMI admitted for arrhythmia monitoring slow or fast (symptomatic) arrhythmias were documented and the need for tape recordings of the ECG was obviated In this patient category a telemetry signal fed into the computer could accomplish monitoring in the ambulatory patient

Nurses opinion on the system

The nurses opinion on the automated system was studied in December 1976 Thirteen nurses participated and all considered that working conditions in the CCU had improved since the introduction of the automated monitoring system However one nurse also thought that the high number of arrhythmias detected had a negative effect by increasing demands on the staff Five out of 10 nurses thought that patient care had improved with the system and the rest considered it unchanged Eight out of 11 considered the ratio of false to true alarms of all kinds acceptable or low whereas three thought this ratio too high

Moderately frequent false highest priority alarms (1 5 per hour for some hours) in a few patients per month have been accepted by the nurses

cases the "true" diagnosis was obtained from the case records or the ECGs recorded on admission

The frequency of highest priority alarms in a few patients with frequent episodes of VT has been disturbing Cancellation of VB monitoring has still resulted in VT alarms generated from the power spectrum analysis or from outstepping HR limits During a 28-month period true VF has occurred in two patients without a correct alarm being given In one of these patients with cardiogenic shock a slow frequency VF occurred terminally and was accompanied by the alarm "check electrodes" In the other what has happened?" was reported due to VF with a low amplitude About 100 VF episodes have been correctly classified during a 2 1/2-year period

Effects on arrhythmia documentation and patient care

The write-outs have been invaluable for arrhythmia documentation However on account of the present study all alarm write-outs were collected and could not be added to the case records In the present version of the system no hard copy report has been obtainable However a special subroutine made it possible to punch out HR, VB frequency and reported alarms for each patient and this feature was utilized in the second evaluation study (II)

Regarding the effect of automated monitoring on patient care it is not possible to say that the prognosis has been improved since the introduction of the system However compared to the ratemeter system previously relied on in the CCU a marked improvement in the quality of ECG monitoring has been brought about with the automated system In view of results from 24 h visual ECG monitoring in other CCUs the high incidence of various arrhythmias found in our CCU (Table X) indicates a high efficiency of the automated monitoring system Thus constant human ECG monitoring does not seem to be necessary with efficient use of the system

Although single episodes of VT were considered an indication for antiarrhythmic treatment in patients with a suspected or a proven AMI several patients with paroxysmal VT of short length did not receive lidocaine by infusion As evaluated from the prognosis in ventricular tachycardia reported in Table XII this restrictive use of the drug did

supraventricular tachycardia (SVT) The lowest priority arrhythmia alarms comprised more than 5 VB/SVBs per min missed QRS bradycardia (HR <50/min) and tachycardia (HR >120/min) Also a number of monitoring status alarms were included in the system

The alarm function during 1 000 h of monitoring (5 million ECG complexes) was evaluated in 55 CCU patients The total alarm time at optimal performance was determined to 134 h for 70% of this time a correct alarm and for 17% an incorrect alarm was present 13% of alarm time was unreported Monitoring status alarms and irrelevant alarms were present for 46 and 6 h respectively In a 4 week study comprising 3 000 monitoring hours also analyzed manually the computer correctly diagnosed 8 out of 24 asystole events 3 out of 4 VF and 31 out of 44 VT episodes Only a few of these arrhythmias were unreported

Several factors influencing the accuracy of the automated arrhythmia analysis have been found The characteristics of the ECG material are of great importance for the performance Negative factors include an irregular basic rhythm the presence of conduction disturbance variability in shapes of normal and ectopic beats and a high noise level Patients with intermittent external pacemaker activity or rate-dependent conduction disturbances produced frequent false alarms These patients comprised about 2% of the total

The alarm write-outs generated by the monitoring system (Program II) contained the arrhythmias from about 90% of the patients with various ventricular and supraventricular rhythms Therefore arrhythmia incidence and prognosis in various arrhythmias were studied during long term use of the system An investigation was performed in 339 patients with proven AMI and in 340 patients without proven AMI All arrhythmias except bradycardia were significantly more common in the AMI group VT and SVT were observed in 38 and 50% of AMI patients respectively In the non-AMI group the corresponding figures were 10 and 22% respectively The mortality in the following arrhythmias was not significantly different between AMI and non-AMI patients asystole VF VT consecutive VBs and R-on-T VBs In AMI the following arrhythmias were associated with a significant increase in mortality: asystole VF extreme bradycardia and tachycardia In the non-AMI group asystole paired VBs and tachycardia were associated

SUMMARY

A multipatient monitoring system for arrhythmia detection in the *CCU* has been developed and evaluated

In the first arrhythmia detector (Program I) ventricular ectopic beats (VBs) were recognized by correlation with a stored fixed VB waveform In a set of test ECGs (50 000 complexes) 94% of true VBs were recognized in sinus rhythm compared to 74% in atrial fibrillation

In the second arrhythmia detector (Program II) a more sophisticated method for beat separation and classification was developed QRST classification was based on a feature extraction scheme utilizing four approximately orthonormal basis functions The waveform of each beat was classified with the aid of two discriminant functions operating on the waveform features of each beat and on rhythm data Similar beats were clustered The classification of ventricular fibrillation (VF) ventricular tachycardia (VT) and asystole was partly based on the power spectrum of the ECG

Program I and II were compared in a beat-by-beat study using taped ECG recordings (about 600 000 beats) from 12 patients with acute myocardial infarction (AMI) Program I and II correctly detected 48 and 60% of all VBs respectively irrelevant VB detections usually caused by noise corresponded to 0 21 and 0 07% of all beats *respectively* *In some special ventricular arrhythmias* (alarms) the ratio of correct irrelevant alarms was 1 3 with Program I and 3 1 with Program II

Program II was implemented in an 8-patient monitoring system taken into routine use in 1976 Communication with the system could be performed at bedside as well as at the nurses station At an alarm a delayed ECG and an arrhythmia diagnosis were presented on a write-out A wireless alarm transmitting system alerted the nurses through small pocket receivers All alarms were grouped into three priority levels The highest level included alarms for asystole VF and VT The second level included alarms for runs of VBs extreme bradycardia (heart rate (HR)<35/min) extreme tachycardia (HR >150/min) idioventricular rhythm paired VBs *R-on-T* VBs ventricular bigeminy and

supraventricular tachycardia (SVT) The lowest priority arrhythmia alarms comprised more than 5 VB/SVBs per min missed QRS bradycardia (HR <50/min) and tachycardia (HR >120/min) Also a number of monitoring status alarms were included in the system

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with a significant increase in mortality AMI patients with paired VBs and/or SVT had a significantly better prognosis in the CCU than those without these arrhythmias AMI patients with 8 or more VBs in succession with a rate >120/min had a poorer CCU and total hospital prognosis than those with no or other runs of VBs Based on the above findings changes in the definitions and priorities of some alarms are suggested

The high incidence of arrhythmias observed in the CCU was probably mainly the result of a high quality of arrhythmia monitoring Constant human ECG monitoring does not seem to be necessary with efficient use of the present system Few technical problems have been encountered during a 2-year period This fact, in combination with a low frequency of false alarms, has contributed to a positive attitude of the nurses towards the system

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